



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | | |
|---|--|---|---|
| (51) International Patent Classification ⁶ : C07D 209/42, 235/24, 403/06, 403/12, 307/85, A61K 31/40, 31/415, C07D 215/54, 453/02, 333/70 | | A2 | (11) International Publication Number: WO 95/04720 |
| (21) International Application Number: PCT/GB94/01741 | | (43) International Publication Date: 16 February 1995 (16.02.95) | |
| (22) International Filing Date: 9 August 1994 (09.08.94) | | | |
| (30) Priority Data: 9316608.0 10 August 1993 (10.08.93) GB 9410688.7 27 May 1994 (27.05.94) GB | | (74) Agent: FISHER, Adrian, John; Carpmaels & Ransford, 43 Bloomsbury Square, London WC1A 2RA (GB). | |
| (71) Applicant (for all designated States except US): JAMES BLACK FOUNDATION LIMITED (GB/GB); 68 Half Moon Lane, Dulwich, London SE24 9JE (GB). | | (81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD). | |
| (72) Inventors; and (75) Inventors/Applicants (for US only): KALINDJIAN, Sarkis, Barret (GB/GB); 45 Colcokes Road, Banstead, Surrey SM7 2EJ (GB). STEEL, Katherine, Isobel, Mary (GB/GB); 162 Lennard Road, Beckenham, Kent BR3 1QP (GB). PETHER, Michael, John (GB/GB); 2 Felstead Road, Orpington, Kent BR6 9AB (GB). DAVIES, Jonathan, Michael, Richard (GB/GB); 8 Yew Tree Road, Beckenham, Kent BR3 4HT (GB). LOW, Caroline, Minli, Rachel (GB/GB); 2 Lyndhurst Close, Croydon, Surrey CR0 5LU (GB). HUDSON, Martin, Lyn (GB/GB); Basement Flat, 6 Montpelier Crescent, Brighton BN1 3JF (GB). BUCK, Idiko, Maria (GB/GB); 99 Holland Walk, London N19 3XU (GB). MCDONALD, | | Published Without international search report and to be republished upon receipt of that report. | |
| (54) Title: GASTRIN AND CCK RECEPTOR LIGANDS | | | |
| (57) Abstract | | | |
| <p>Compounds of formula (Ia), (Ib) or (Ic), wherein A represents a group having two fused rings, or a group of formula (Id), R¹_(m) represents up to 6 substituents, K represents -O-, -S-, -CH₂-, -N(R²-) or -N(COR²-), in which R² is H or C₁ to C₃ alkyl, W is a carbonyl, sulphonyl or sulphinyl group, and X is a carbonyl, sulphonyl or sulphinyl group, provided that at least one of W and X contains carbonyl, Y and Z are as given in the description and their pharmaceutically acceptable salts are ligands at CCK and/or gastrin receptors.</p> | | | |
| <p>(Ia)</p> | | <p>(Ic)</p> | |
| <p>(Ib)</p> | | <p>(Id)</p> | |

THIS PAGE BLANK (USPTO)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | |
|----|--------------------------|----|---------------------------------------|----|--------------------------|
| AT | Austria | GB | United Kingdom | MR | Mauritania |
| AU | Australia | GE | Georgia | MW | Malawi |
| BB | Barbados | GN | Guinea | NE | Niger |
| BE | Belgium | GR | Greece | NL | Netherlands |
| BF | Burkina Faso | HU | Hungary | NO | Norway |
| BG | Bulgaria | IE | Ireland | NZ | New Zealand |
| BJ | Benin | IT | Italy | PL | Poland |
| BR | Brazil | JP | Japan | PT | Portugal |
| BY | Belarus | KE | Kenya | RO | Romania |
| CA | Canada | KG | Kyrgyzstan | RU | Russian Federation |
| CF | Central African Republic | KP | Democratic People's Republic of Korea | SD | Sudan |
| CG | Congo | KR | Republic of Korea | SE | Sweden |
| CH | Switzerland | KZ | Kazakhstan | SI | Slovenia |
| CI | Côte d'Ivoire | LI | Liechtenstein | SK | Slovakia |
| CM | Cameroon | LT | Lithuania | SN | Senegal |
| CN | China | LU | Luxembourg | TD | Chad |
| CS | Czechoslovakia | LV | Latvia | TG | Togo |
| CZ | Czech Republic | MC | Monaco | TJ | Tajikistan |
| DE | Germany | MD | Republic of Moldova | TT | Trinidad and Tobago |
| DK | Denmark | MG | Madagascar | UA | Ukraine |
| ES | Spain | ML | Mali | US | United States of America |
| FI | Finland | MN | Mongolia | UZ | Uzbekistan |
| FR | France | | | VN | Viet Nam |
| GA | Gabon | | | | |

Gastrin and CCK Receptor Ligands

This invention relates to gastrin and CCK receptor ligands. The invention also relates to methods for preparing such
5 ligands and to compounds which are useful as intermediates in such methods.

Gastrin and the CCK's are structurally-related neuropeptides which exist in gastrointestinal tissue and in the CNS (see
10 Mutt V., Gastrointestinal Hormones, Glass G.B.J., ed., Raven Press, N.Y., p 169 and Nisson G., ibid, p. 127).

Gastrin is one of the three primary stimulants of gastric acid secretion. Several forms of gastrin are found
15 including 34-, 17-, and 14-amino acid species with the minimum active fragment being the C-terminal tetrapeptide (TrpMetAspPhe-NH₂) which is reported in the literature to have full pharmacological activity (see Tracey H.J. and Gregory R.A., Nature (London), 1964, 204, 935). Much effort
20 has been devoted to the synthesis of analogues of this tetrapeptide (and the N-protected derivative Boc-TrpMetAspPhe-NH₂) in an attempt to elucidate the relationship between structure and activity.

25 Natural cholecystokinin is a 33 amino acid peptide (CCK-33), the C-terminal 5 amino acids of which are identical to those of gastrin. Also found naturally is the C-terminal octapeptide (CCK-8) of CCK-33.

30 The cholecystokinins are reported to be important in the regulation of appetite. They stimulate intestinal motility, gall bladder contraction, pancreatic enzyme secretion, and are known to have a trophic action on the pancreas. They also inhibit gastric emptying and have various effects in
35 the CNS.

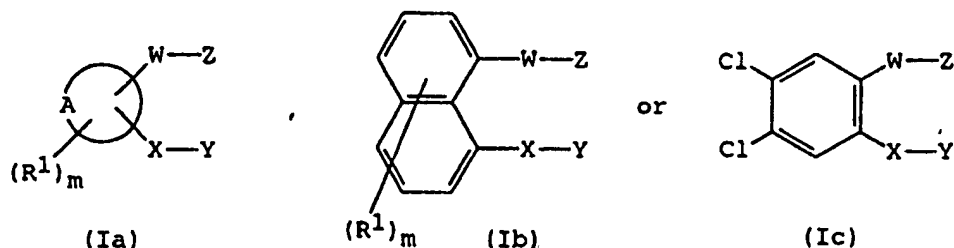
Compounds which bind to cholecystokinin and/or gastrin receptors are important because of their potential

pharmaceutical use as antagonists of the natural peptides.

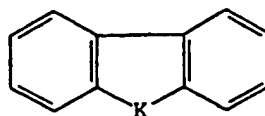
A number of gastrin antagonists have been proposed for various therapeutic applications, including the prevention of gastrin-related disorders, gastrointestinal ulcers, Zollinger-Ellison syndrome, antral G cell hyperplasia and other conditions in which lowered gastrin activity is desirable. The hormone has also been shown to have a trophic action on cells and so an antagonist may be expected to be useful in the treatment of cancers, particularly in the stomach and the colon.

Possible therapeutic uses for cholecystokinin antagonists include the control of appetite disorders such as anorexia nervosa, and the treatment of pancreatic inflammation, biliary tract disease and various psychiatric disorders. Other possible uses are in the potentiation of opiate (e.g. morphine) analgesia, and in the treatment of cancers, especially of the pancreas. Moreover, ligands for cholecystokinin receptors in the brain (so-called CCK₁ receptors) have been claimed to possess anxiolytic activity.

According to the present invention, there are provided compounds of the formula



wherein A represents a bicyclic group (meaning a group having two fused rings, in which the atoms which are common to the two rings are joined by a single or multiple bond), W and X replacing hydrogen on adjacent atoms (most usually adjacent carbon atoms), or A is a group of the formula



(Id)

in which W and X replace hydrogen on adjacent carbon atoms,

- 5 m is from 0 to 6, provided that m is not more than 2 unless R¹ is exclusively halo,

R¹ is halo, amino, amidino, nitro, cyano, hydroxy, sulphamoyl, hydroxysulphonyl, carboxy, esterified carboxy, amidated carboxy, tetrazolyl, C₁ to C₆ alkyl (particularly C₁ to C₆ alkyl), aryl, substituted aryl, C₁ to C₆ hydroxyalkyl, C₁ to C₆ haloalkyl, C₁ to C₆ alkoxy, C₁ to C₆ alkylcarboxyamino, HON=C-, R²⁷-SO₂-NH-, R²⁷-SO₂-NH-CO-, R²⁷-CO-, R²⁷-CO-NH-, R²⁷-CO-NH-SO₂-, R²⁷-CO-NH-SO- or R²⁸-NH-SO₂-, wherein R²⁷ is H (except when R²⁷ is attached to a sulphur atom), C₁ to C₆ alkyl, C₁ to C₆ haloalkyl, aryl or substituted aryl, and R²⁸ is H, C₁ to C₆ alkyl, C₁ to C₆ haloalkyl, aryl, substituted aryl, -OH or -CN (each R¹ group, when m is 2 or more, being independently selected from the foregoing),

K represents -O-, -S-, -CH₂-, -N(R²)- or -N(COR²)-, in which R² is H or C₁ to C₆ alkyl,

- 25 W is a carbonyl, sulphonyl or sulphinyl group, and X is a carbonyl, sulphonyl or sulphinyl group, provided that at least one of W and X contains carbonyl,

Y is R³-N(R⁴)- or R³'-O- (wherein R³ is H or C₁ to C₁₅ hydrocarbyl, one or more hydrogen atoms of the hydrocarbyl moiety optionally being replaced by halogen atoms, and up to two carbon atoms of the hydrocarbyl moiety optionally being replaced by a nitrogen, oxygen or sulphur atom, R³'

is C₆ to C₁₅ hydrocarbyl, one or more hydrogen atoms of the hydrocarbyl moiety optionally being replaced by halogen atoms, and up to two carbon atoms of the hydrocarbyl moiety optionally being replaced by a nitrogen, oxygen or sulphur atom, and R⁴ is H, C₁ to C₃ alkyl, carboxymethyl or esterified carboxymethyl), provided that Y does not contain a -O-O- group, and

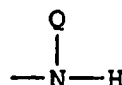
Z is selected from

10

i) -O-R^5

wherein R⁵ is H, C₁ to C₅ alkyl, phenyl, substituted phenyl, benzyl or substituted benzyl;

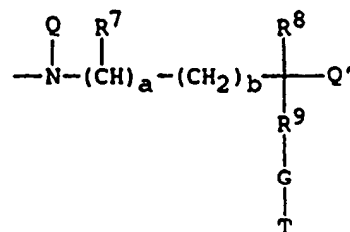
15 ii)



wherein Q is H, C₁ to C₅ hydrocarbyl, or -R⁶-U, wherein R⁶ is a bond or C₁ to C₅ (eg. C₁ to C₃) alkylene and U is aryl, substituted aryl, heterocyclic, substituted heterocyclic or cycloalkyl (preferably cyclohexyl or cycloheptyl),

20

iii)



wherein a is 0 or 1 and b is from 0 to 3,

25

R⁷ is H or methyl,

R⁸ is H or methyl; or R⁸ is CH₂= and Q' is absent; or R⁷ and R⁸ are linked to form a 3- to 7-membered ring,

R⁹ is a bond or C₁ to C₃ hydrocarbylene,

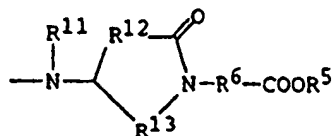
G is a bond, -CHOH- or -C(O)-

- 5 Q' is as recited above for Q or -R⁶-(C(O))_d-L-(C(O))_e-R⁵
 (wherein R⁵ and R⁶ are as defined above, L is O, S or
 -N(R¹⁰)-, in which R¹⁰ is as defined above for R⁴, and d
 and e are 0 or 1, provided that d+e<2); or Q' and R⁸,
 10 together with the carbon atom to which they are
 attached, form a 3- to 7-membered ring,

- Q is as defined above; or Q and R⁸ together form a group
 of the formula -(CH₂)_f-V-(CH₂)_g- wherein V is -S-, -S(O)-,
 -S(O)₂-, -CH₂-, -CHOH- or -C(O)-, f is from 0 to 2 and g
 15 is from 0 to 3; or, when Q' is -R⁶-U and U is an aromatic
 group, Q may additionally represent a methylene link to
 U, which link is ortho to the R⁶ link to U,

- T is H, cyano, C₁ to C₄ alkyl, -CH₂OH, carboxy, esterified
 20 carboxy, amidated carboxy or tetrazolyl; or

iv)



- 25 wherein R⁵ and R⁶ are as defined above, R¹¹ is as defined
 above for R⁴, and R¹² and R¹³ are independently a
 bond or C₁ to C₃ alkylene, provided that R¹² and
 R¹³ together provide from 2 to 4 carbon atoms in
 the ring,

- 30 and pharmaceutically acceptable salts thereof.

Certain compounds of the invention exist in various
 regioisomeric, enantiomeric, tautomeric and diastereomeric
 forms. It will be understood that the invention comprehends

the different regioisomers, enantiomers, tautomers and diastereomers in isolation from each other, as well as mixtures.

- 5 The term "hydrocarbyl", as used herein, refers to monovalent groups consisting of carbon and hydrogen. Hydrocarbyl groups thus include alkyl, alkenyl, and alkynyl groups (in both straight and branched chain forms), cycloalkyl (including polycycloalkyl), cycloalkenyl, and aryl groups,
10 and combinations of the foregoing, such as alkylaryl, alkenylaryl, alkynylaryl, cycloalkylaryl, and cycloalkenylaryl groups,

- A "carbocyclic" group, as the term is used herein, comprises
15 one or more closed chains or rings, which consist entirely of carbon atoms. Included in such groups are alicyclic groups (such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and adamantyl), groups containing both alkyl and cycloalkyl moieties (such as adamantanemethyl), and aromatic
20 groups (such as phenyl, naphthyl, indanyl, fluorenyl, (1,2,3,4)-tetrahydronaphthyl, indenyl and isoindenyl). The term "aryl" is used herein to refer to aromatic carbocyclic groups, including those mentioned above.

- 25 A "heterocyclic" group comprises one or more closed chains or rings which have at least one atom other than carbon in the closed chain or ring. Examples include benzimidazolyl, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl,
30 imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, piperazinyl, morpholinyl, thionaphthyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl,
35 isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl and carbolinyl.

The term "halogen", as used herein, refers to any of fluorine, chlorine, bromine and iodine. Most usually, however, halogen substituents in the compounds of the invention are chlorine or fluorine substituents.

5

When reference is made herein to a "substituted" aromatic group, the substituents will generally be from 1 to 3 in number (and more usually 1 or 2 in number), and generally selected from the groups recited above for R¹. However,
10 halo substituents may be up to 5 in number.

Preferably, m is 0. However, when m is not 0, R¹ is preferably selected from halo, amino, nitro, cyano, sulphamoyl, sulphonyl, trifluoromethyl, C₁ to C₃ alkyl,
15 hydroxy, C₁ to C₃ hydroxyalkyl, C₁ to C₃ alkoxy, C₁ to C₃ alkylcarboxyamino, carboxy, esterified carboxy, amidated carboxy and tetrazolyl, and more preferably from halo, amino, nitro, cyano, sulphamoyl, C₁ to C₃ alkyl and C₁ to C₃ alkoxy. As mentioned above, when m is 2 or more, each R¹
20 group is independent of the others. For example, the compounds of the invention may include two different R¹ groups.

An "esterified" carboxy group, as the term is used herein,
25 is preferably of the form -COOR¹⁴, wherein R¹⁴ is C₁ to C₃ alkyl, phenyl, substituted phenyl, benzyl, substituted benzyl, indanyl, or one of the following:

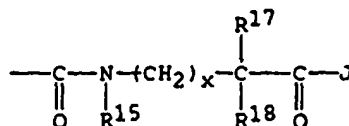


30 Most commonly, R¹⁴ is C₁ to C₃ alkyl, benzyl or substituted benzyl, and particularly C₁ to C₃ alkyl.

"Amidated" carboxy groups include alkoxyamido groups (particularly C₁ to C₃ alkoxyamido groups), but are more
35 usually of the form -CONR¹⁵R¹⁶ wherein R¹⁵ is H, C₁ to C₃,

alkyl, phenyl, substituted phenyl, benzyl or substituted benzyl, and R^{16} is -OH or one of the groups just recited for R^{15} .

- 5 In the case of the group T, preferred amidated carboxy groups take the form $-\text{CONR}^{15}\text{R}^{16}$ (wherein R^{15} and R^{16} are as defined above) or



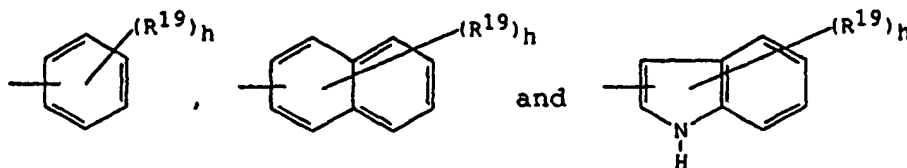
- 10 wherein R^{15} is as defined above, R^{17} and R^{18} are independently H or methyl, or R^{17} and R^{18} (together with the carbon atom to which they are attached) form a 3- to 7-membered carbocyclic group, J is -OH, -O- R^{14} or -NHR 16 , wherein R^{14} and R^{16} are as defined above, and x is 0 to 3.

15

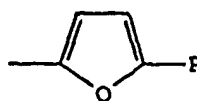
When R^7 and R^8 are linked to form a ring, such ring will generally be saturated, and usually also carbocyclic. Similarly, when Q' and R^8 are linked to form a ring, this will also usually be saturated and carbocyclic.

20

Exemplary carbocyclic and heterocyclic groups which may form the group U include:

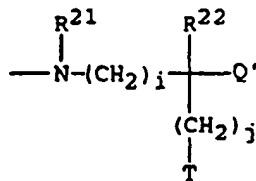


- wherein R^{19} is as defined above for R^1 , and h is from 0 to 3
 25 (or up to 5 when R^{19} is exclusively halo), and



wherein P is H or $-\text{COOR}^{20}$, in which R^{20} is as defined above for R^{15} .

2 is preferably -NH_2 , -O-R^5 or



wherein i is from 0 to 4, j is from 0 to 3, R^{21} and R^{22} are independently H or methyl, or R^{21} and R^{22} together form a group of the formula $\text{---(CH}_2\text{)}_k\text{---V'---CH}_2\text{---}$ (wherein V' is $\text{---CH}_2\text{---}$, ---CHOH--- or ---C(O)--- , and k is 0 to 2). Most commonly, i is 0 or 1 and j is 0 to 2.

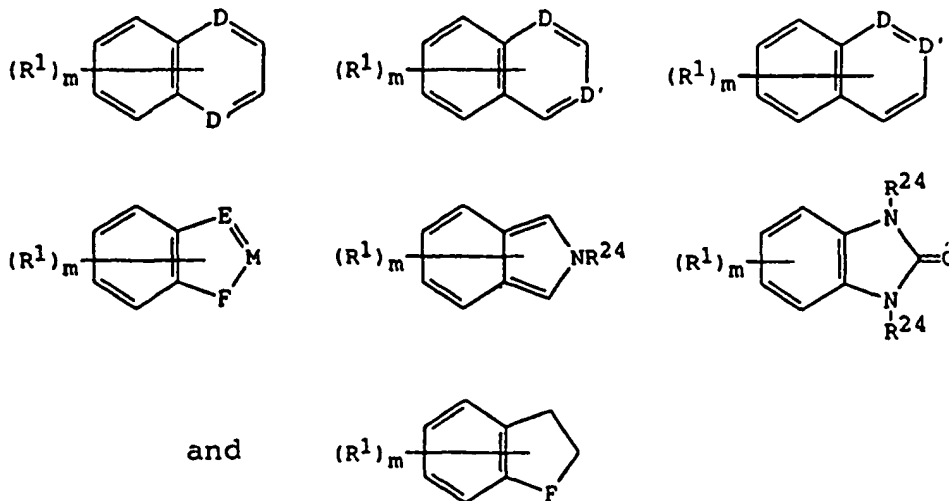
When W is sulphonyl, Y is preferably $\text{R}^3\text{---NH---}$.

10

Preferably, R^3 is C_6 to C_8 straight or branched chain alkyl, or $\text{R}^{23}\text{---(CH}_2\text{)}_p\text{---}$, wherein R^{23} is selected from phenyl, 1-naphthyl, 2-naphthyl, indolyl, norbornyl, adamantyl, cyclohexyl or cycloheptyl, and p is from 0 to 3.

15

Favoured bicyclic groups to form A in formula (Ia) above include



wherein R^{24} is H, C_1 to C_8 alkyl or $\text{R}^{25}\text{---CO---}$

20 R^{25} is H or C_1 to C_8 (eg. C_1 to C_3) alkyl

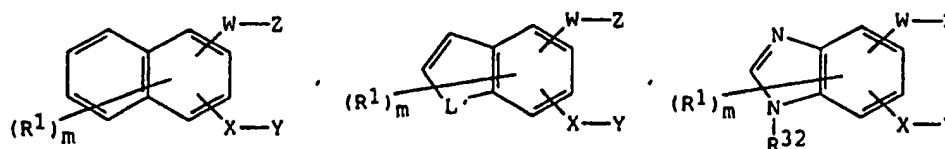
D and D' are independently -CH=, -N= or -SR²⁶= (R²⁶ being H or C₁ to C₃ alkyl, or R²⁶ is absent and the sulphur atom is positively charged)

5 E is -CH= or -N=

M is -CR²⁴=, -N= or -C(NR²⁴R²⁵)= (wherein R²⁴ and R²⁵ are as defined above), and

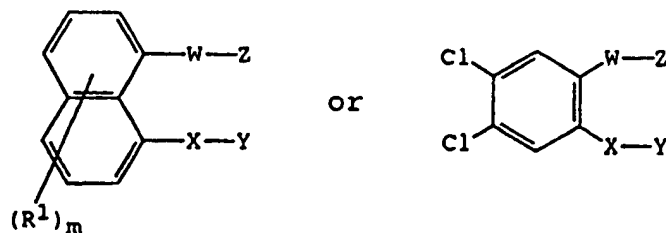
10 F is -O-, -S-, -CH₂- or -NR²⁴- (wherein R²⁴ is as defined above).

Preferably, the compounds of the invention are of the formula:



15

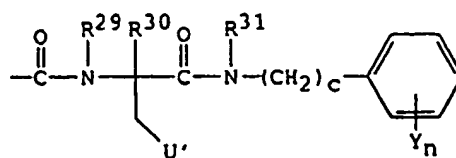
(wherein W and X are attached to adjacent carbon atoms; R³² is H, C₁ to C₃ alkyl or C₁ to C₃ alkylcarboxy; and L' is -NR³²-, -O- or -S-),



20 Also preferred are compounds in which

-X-Y is -CONR³R⁴ (R³ and R⁴ being as defined above), and

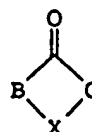
-W-Z is



(wherein R^{29} , R^{30} and R^{31} are independently H or C_1 to C_3 alkyl; U' is an (optionally substituted) aromatic group; n is 1 or 2; Y is $-CO_2H$, tetrazolyl, esterified carboxy, amidated carboxy, $R^{27}-SO_2-NH-$, $R^{27}-SO_2-NH-CO-$, $R^{27}-CO-$, $R^{27}-CO-NH-$, $R^{27}-CO-NH-SO_2-$, $R^{27}-CO-NH-SO-$ or $R^{28}-NH-SO_2-$ (R^{27} and R^{28} being as defined above), each Y being independently selected from the foregoing when n is 2; and c is from 0 to 2).

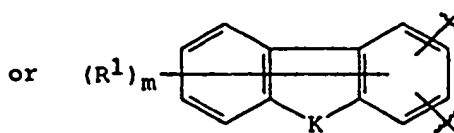
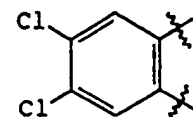
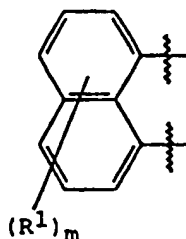
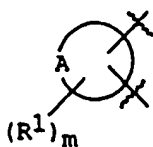
10

Compounds according to the present invention in which W is a carbonyl group, X is carbonyl or sulphonyl, and Z is OH may conveniently be made by reacting a compound of the formula YH (ie. either an alcohol or an amine) with a compound of the formula



(II)

wherein B represents



If YH is an amine, the reaction is suitably carried out in a solvent such as THF in the presence of a base such as

DMAP. If YH is an alcohol, the reaction may be conducted in pyridine at elevated temperature.

Compounds in which Z is other than OH may of course be made
5 from the acid compound



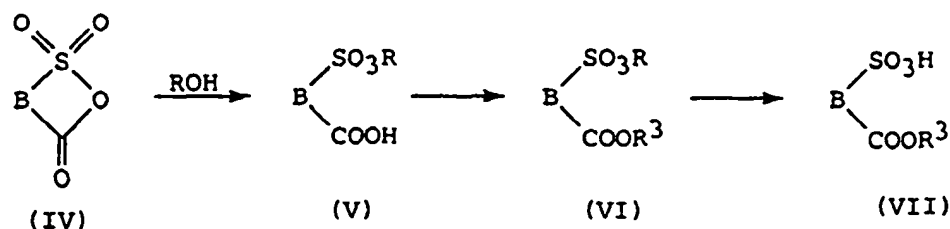
by conventional esterification or amidation reactions on suitably protected derivatives. Suitable amidation methods are described in detail in "The Peptides, Vol. 1", Gross and
10 Meinenhofer, Eds., Academic Press, N.Y., 1979. These include the carbodiimide method (using, for example, 1,3-dicyclohexylcarbodiimide [DCC] or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride [EDCI], and optionally an additive such as 1-hydroxybenzotriazole [HOBT] to prevent
15 racemization), the azide method, the mixed anhydride method, the symmetrical anhydride method, the acid chloride method, the acid bromide method, the use of bis (2-oxo-3-oxazolidinyl) phosphinic chloride [BOP-Cl], the use of PyBOP or PyBrOP, the use of the isopropenylsuccinimido carbonate
20 method and the active ester method (using, for example, N-hydroxysuccinimide esters, 4-nitrophenyl esters or 2,4,5-trichlorophenol esters). The coupling reactions are generally conducted under an inert atmosphere, such as an atmosphere of nitrogen or argon. Suitable solvents for the
25 reactants include methylene chloride, tetrahydrofuran [THF], dimethoxyethane [DME] and dimethylformamide [DMF].

Bisamides according to the present invention may alternatively be prepared by reacting a compound of formula
30 (II) with a suitably protected derivative of ZH, followed by conventional amidation as described above.

An analogous procedure may also be used as the basis for preparing the compounds of the invention in which W is
35 sulphonyl and Y is R³-O-, as depicted in reaction scheme A

below:

Reaction Scheme A

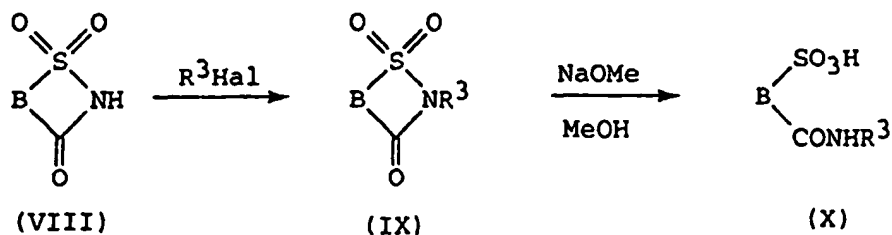


In this case, the mixed anhydride (IV) is opened with an alcohol such as benzyl alcohol (represented as ROH), so that the product is the corresponding sulphonyl ester (V). The free carboxylic acid group of this sulphonyl ester may then be esterified by conventional methods, followed by hydrogenolysis of the product (VI) to yield the desired sulphonic acid carboxylic ester (VII).

The compounds of the invention in which W is sulphonyl and Y is R³-NH- may be prepared by analogous means, in which compound (V) is amidated (rather than esterified) prior to hydrogenolysis. Alternatively, a process such as is depicted in reaction scheme B may be employed:

15

Reaction Scheme B



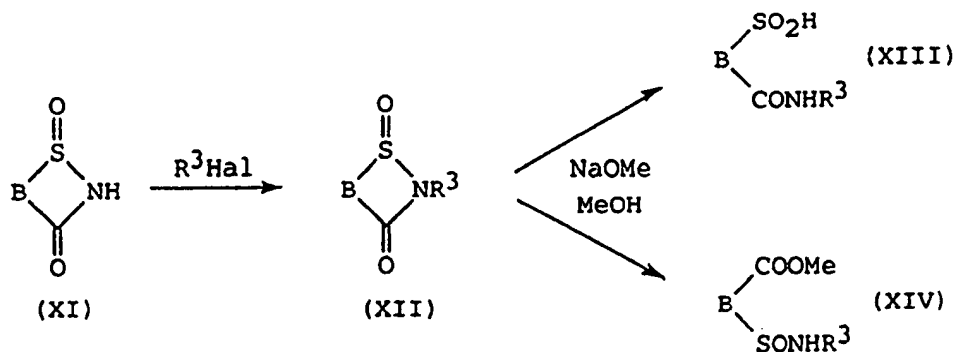
In this scheme, compound (VIII) is reacted with a compound of the formula R³-Hal (wherein Hal represents a halogen atom) to form compound (IX). The N-containing ring may then be opened using an alkoxide (eg. sodium methoxide in

methanol) to produce the target compound (X).

The invention therefore also provides a method of making compounds wherein W is sulphonyl and Y is R³-NH-, said
 5 method comprising the step of reacting a compound of formula (VIII) with a compound of the formula R³-Hal, and then reacting the product with an alkoxide.

Compounds of the invention wherein W or X is a sulphoxide
 10 group may conveniently be prepared by the route shown in reaction scheme C:

Reaction Scheme C



Compound (XII) can then be opened both ways to give on the one hand the sulphinamide acid alkyl ester (XIII), and on the other the sulphinic acid amide (XIV). The free sulphinamide acid can of course be obtained from the alkyl
 5 ester (XIII) by conventional methods.

Accordingly, the invention also provides a method of making compounds wherein W or X is sulphoxide, said method comprising the step of reacting a compound of formula (XI)
 10 with a compound of the formula R³-Hal, and then reacting the product with an alkoxide.

While reaction schemes B and C above lead to the free sulphonic or sulphinic acid compounds, it will be

appreciated that the corresponding ester or amide derivatives can be prepared from the free acid compounds by conventional methods. Most usually, coupling of the sulphonic or sulphinic acid compounds will be via the
5 corresponding sulphonic or sulphinic acid chlorides.

Pharmaceutically acceptable salts of the acidic or basic compounds of the invention can of course be made by conventional procedures, such as by reacting the free base
10 or acid with at least a stoichiometric amount of the desired salt-forming acid or base.

The compounds of the invention can be administered by oral or parenteral routes, including intravenous, intramuscular,
15 intraperitoneal, subcutaneous, rectal and topical administration.

For oral administration, the compounds of the invention will generally be provided in the form of tablets or capsules or
20 as an aqueous solution or suspension.

Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating
25 agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch
30 and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

35

Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules wherein the active ingredient is mixed

with water or an oil such as peanut oil, liquid paraffin or olive oil.

For intramuscular, intraperitoneal, subcutaneous and
5 intravenous use, the compounds of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions according to
10 the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinylpyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

15

Effective doses of the compounds of the present invention may be ascertained by conventional methods. The specific dosage level required for any particular patient will depend on a number of factors, including the severity of the
20 condition being treated and the weight of the patient. In general, however, the daily dose (whether administered as a single dose or as divided doses) will be in the range 0.001 to 5000 mg per day, and more usually from 1 to 1000 mg per day. Expressed as dosage per unit body weight, a typical
25 dose will be between 0.01 µg/kg and 50mg/kg, eg between 10 µg/kg and 10 mg/kg.

The invention is now further illustrated by means of the following examples.

30

Example 1 3-(1-adamantanemethylaminocarbonyl)-2-naphthoic acid

2,3-naphthalenedicarboxylic anhydride (198 mg, 1.0 mmol) and
35 1-adamantanemethylamine (176 mg, 1.0 mmol) were dissolved in dry THF (5 ml) and stirred at room temperature for 1h. A thick white precipitate was formed and this was isolated by filtration and washed with ether to leave the title compound

(229 mg, 69%), ^1H NMR (d^6 -DMSO) δ 12.9 (1H, s), 8.3 (2H, s), 8.1 (2H, t), 7.9 (1H, s), 7.6 (2H, m), 2.9 (2H, d), 1.9 (3H, s), 1.6 (6H, q), 1.5 (6H, s).

- 5 The material was further characterised and tested as the N-methyl-D-glucamine salt found: C, 62.36; H, 7.77; N, 4.60. $\text{C}_{30}\text{H}_{42}\text{N}_2\text{O}_8 \cdot \text{H}_2\text{O}$ requires C, 62.48; H, 7.69; N, 4.85%

10 Example 2 2-(1S-methoxycarbonyl-ethylaminocarbonyl)-3-(1-adamantanemethylaminocarbonyl)-naphthalene

3-(1-adamantanemethylaminocarbonyl)-2-naphthoic acid (229 mg, 0.52 mmole) (the compound of example 1) and PyBOP (312
15 mg, 0.6 mmole) were taken up in dry dichloromethane (5 ml) and Hunigs base (0.32 ml, 1.5 mmole) was added. The reaction mixture was stirred under an atmosphere of dry argon for 1h. L-alanine methyl ester hydrochloride (80 mg, 0.6 mmole) was added and the mixture stirred overnight. The organic layer
20 was washed with 5% potassium hydrogensulphate (5 ml), sodium hydrogencarbonate (5 ml) and saturated brine (5 ml). It was then dried, filtered and evaporated to leave the crude title compound which was further purified by column chromatography (silica 4% methanol and 96% dichloromethane. The title
25 compound (194 mg, 67%) was isolated as a white solid, m.p. 136-8°, found: C, 69.68; H, 7.17; N, 6.04. $\text{C}_{27}\text{H}_{32}\text{N}_2\text{O}_4 \cdot \text{H}_2\text{O}$ requires C, 69.51; H, 7.34; N, 6.00% ^1H NMR (CDCl_3) δ 8.0 (1H, s), 7.9 (1H, s), 7.8 (2H, m), 7.6 (3H, m), 7.0 (1H, t), 4.8 (1H, m), 3.8 (3H, s), 3.2 (2H, m), 2.0 (3H, s), 1.8 (6H,
30 q), 1.6 (6H, s), 1.5 (3H, d).

Example 3 3-(2R-carboxypyrrolidino-carbonyl)-2-(1-adamantanemethylaminocarbonyl)-naphthalene

- 35 a. 3-(2R-benzyloxycarbonyl-pyrrolidino-carbonyl)-2-(1-adamantanemethylaminocarbonyl)-naphthalene

The material was made essentially as in example 2 except

that D-proline benzyl ester hydrochloride was used as substrate instead of L-alanine methyl ester hydrochloride.

b. 3-(2R-carboxy-pyrrolidino-carbonyl)-2-(1-adamantane-5 methylaminocarbonyl)-naphthalene

The product of step a (195 mg, 0.35 mmol) was dissolved in THF (5 ml) and 10% palladium on charcoal (20 mg) was added. The reaction mixture was stirred overnight under an atmosphere of hydrogen and then filtered through celite and evaporated to yield the title compound (121 mg, 76%), ¹H NMR (d⁶-DMSO) δ 12.6 (1H, s), 8.4 (1H, t), 8.2-7.5 (6H, m), 4.3 (1H, m), 3.6-2.2 (6H, m), 2.0 (2H, m), 1.8 (3H, s), 1.5 (6H, q), 1.4 (6H, s).

15

The material was further characterised and tested as the N-methyl-D-glucamine salt found: C, 60.00; H, 7.60; N, 5.85. C₃₅H₄₉N₃O₉.2.4 H₂O requires C, 60.12; H, 7.76; N, 6.00%

20 Example 4 2-(2S-carboxypyrrolidino-carbonyl)-3-(1-adamantanemethylaminocarbonyl)-naphthalene

The material was prepared essentially as in example 3 except that L-proline benzyl ester hydrochloride was used in step a instead of D-proline benzyl ester hydrochloride, ¹H NMR (d⁶-DMSO) δ 12.6 (1H, s), 8.4 (1H, t), 8.2-7.5 (6H, m), 4.3 (1H, m), 3.6-2.2 (6H, m), 2.0 (2H, m), 1.8 (3H, s), 1.5 (6H, q), 1.4 (6H, s).

30 The material was further characterised and tested as the N-methyl-D-glucamine salt found: C, 61.62; H, 6.98; N, 6.09. C₃₅H₄₉N₃O₉.0.45 DCM requires C, 61.35; H, 7.24; N, 6.05%

35 Example 5 2-(1R-carboxyethylamino-carbonyl)-3-(1-adamantanemethylaminocarbonyl)-naphthalene

The material was prepared essentially as in example 3 except that D-alanine benzyl ester hydrochloride was used in step

a instead of D-proline benzyl ester hydrochloride, ^1H NMR (d^6 -DMSO) δ 12.6 (1H, s), 8.7 (1H, d), 8.3 (1H, t), 8.1-7.5 (6H, m), 4.4 (1H, m), 2.9 (2H, 2xdd), 1.9 (3H, s), 1.6 (6H, q), 1.5 (6H, s), 1.3 (3H, d).

5

The material was further characterised and tested as the N-methyl-D-glucamine salt found: C, 61.52; H, 7.54; N, 6.92. $\text{C}_{33}\text{H}_{47}\text{N}_3\text{O}_9 \cdot 0.9 \text{H}_2\text{O}$ requires C, 61.87; H, 7.58; N, 6.56%

10 Example 6 2-(2S-methoxycarbonylpyrrolidino-carbonyl)-3-(1-adamantanemethylaminocarbonyl)-naphthalene

The compound of example 4 (88 mg, 0.18 mmol) was dissolved in diethyl ether (30 ml) and an ethereal solution of
15 diazomethane was added until the solution remained yellow. Acetic acid was added to quench the reaction and the solvent was removed by evaporation the last traces by azeotrope with dichloromethane. The solid was dried in vacuo to leave the title compound (61 mg, 67 %). found: C, 62.46; H, 6.55; N,
20 5.19. $\text{C}_{29}\text{H}_{34}\text{N}_2\text{O}_4 \cdot 1.22 \text{DCM}$ requires C, 62.77; H, 6.35; N, 4.84% ^1H NMR (d^6 -DMSO) δ 8.4 (1H, t), 8.2-7.5 (6H, m), 4.4 (1H, m), 3.7 (3H, s), 3.6-2.2 (6H, m), 2.0 (2H, m), 1.8 (3H, s), 1.5 (6H, q), 1.4 (6H, s).

25 Example 7 2-(2R-methoxycarbonylpyrrolidino-carbonyl)-3-(1-adamantanemethylaminocarbonyl)-naphthalene

The compound was prepared as in example 6 except that, the compound of example 3 was used as substrate instead of the
30 compound of example 4. found: C, 69.96; H, 7.06; N, 5.68. $\text{C}_{29}\text{H}_{34}\text{N}_2\text{O}_4 \cdot 1.16 \text{H}_2\text{O}$ requires C, 70.30; H, 7.39; N, 5.65% ^1H NMR (d^6 -DMSO) δ 8.4 (1H, t), 8.2-7.5 (6H, m), 4.4 (1H, m), 3.7 (3H, s), 3.6-2.2 (6H, m), 2.0 (2H, m), 1.8 (3H, s), 1.5 (6H, q), 1.4 (6H, s).

35

Example 8 2-(1R-methoxycarbonylethylamino-carbonyl)-3-(1-adamantanemethylaminocarbonyl)-naphthalene

The compound was prepared as in example 6 except that the compound of example 5 was used as substrate instead of the compound of example 4. found: C, 71.78; H, 7.37; N, 6.40. $C_{27}H_{32}N_2O_4 \cdot 0.12 H_2O$ requires C, 71.95; H, 7.21; N, 6.21% 1H NMR (d⁶DMSO) δ 8.8 (1H, d), 8.3 (1H, t), 8.1 (1H, s), 7.8 (2H, m), 7.5 (3H, m), 4.4 (1H, m), 3.7 (3H, s), 2.9 (2H, 2 x dd), 1.9 (3H, s), 1.6 (6H, q), 1.5 (6H, s), 1.4 (3H, d).

Example 9 2-(2R-carboxypyrrolidino-carbonyl)-3-(1-
10 adamantanemethyl(N-methyl)aminocarbonyl)-naphthalene

a. 3-(1-adamantanemethyl(N-methyl)aminocarbonyl)-2-naphthoic acid

15 This was prepared essentially as in example 1 except that N-methyl-1-adamantanemethylamine was used as substrate instead of 1-adamantanemethylamine.

b. 2-(2R-carboxypyrrolidino-carbonyl)-3-(1-adamantane-
20 methyl(N-methyl)aminocarbonyl)-naphthalene

The compound was prepared essentially as in example 3 except that the compound prepared in step a above was used as substrate instead of the compound of example 1 in step a ,
25 1H NMR (d⁶-DMSO) δ 12.6 (1H, s), 8.1-7.3 (6H, m), 4.3 (1H, m), 3.6-2.2 (6H, m), 2.86 and 2.84 (3H, 2 x s), 2.0 (2H, m), 1.8 (3H, s), 1.5 (6H, q), 1.4 (6H, s).

The material was further characterised and tested as the N-methyl-D-glucamine salt found: C, 61.17; H, 7.98; N, 5.14. $C_{36}H_{51}N_3O_9 \cdot 1.3 H_2O \cdot 1.4$ dioxan requires C, 61.19; H, 8.00; N, 5.15%

Example 10 2-(2R-(1R-carboxyethylaminocarbonyl)pyrrolidino-
35 carbonyl)-3-(1-adamantanemethylaminocarbonyl)-naphthalene

a. 2-(2R-(1R-benzyloxycarbonylethylaminocarbonyl)-pyrrolidino-carbonyl)-3-(1-adamantanemethylaminocarbonyl)-

naphthalene

The compound of example 3 (100 mg, 0.22 mmole) and PyBOP (113 mg, 0.22 mmole) were taken up in dry dichloromethane (20 ml) and Hunigs base (0.115 ml, 0.66 mmole) was added. The reaction mixture was stirred under an atmosphere of dry argon for 1h. D-alanine benzyl ester PTSA salt (76.3 mg, 0.22 mmole) was added and the mixture stirred overnight. The organic layer was washed with 5% potassium hydrogensulphate (5 ml), sodium hydrogencarbonate (5 ml) and saturated brine (5 ml). It was then dried, filtered and evaporated to leave the crude title compound which was further purified by column chromatography (silica and ethyl acetate). The title compound (119 mg, 88%) was isolated as a white solid.

15

b. 2-(2R-(1R-carboxyethylaminocarbonyl)pyrrolidinocarbonyl)-3-(1-adamantanemethylaminocarbonyl)-naphthalene

The compound was prepared as in example 3 step b except that the product of step a above was used as substrate, instead of the product of example 3 step a. ¹H NMR (d⁶-DMSO) δ 12.6 (1H, s), 8.6 (1H, m), 8.4 (1H, t), 8.3-7.5 (6H, m), 4.4-3.9 (2H, m), 3.6-3.2 (4H, m), 2.9 (2H, m), 2.0 (2H, m), 1.8 (3H, s), 1.5 (6H, q), 1.4 (6H, s), 1.3 (3H, d).

25

The material was further characterised and tested as the N-methyl-D-glucamine salt

Example 11 2-(2R-carboxymethylaminocarbonylpyrrolidinocarbonyl)-3-(1-adamantanemethylaminocarbonyl)-naphthalene

The compound was prepared essentially as in example 10 except that the 4-toluene sulphonic acid salt of glycine benzyl ester was used as substrate in step a instead of the 4-toluene sulphonic acid salt of D-alanine benzyl ester ¹H NMR (d⁶-DMSO) δ 12.6 (1H, s), 8.6 (1H, m), 8.4 (1H, t), 8.3-7.5 (6H, m), 4.4-4.2 (1H, m), 3.9-3.2 (6H, m), 2.9 (2H, m),

2.1 (2H, m), 1.8 (3H, s), 1.5 (6H, q), 1.4 (6H, s).

The material was further characterised and tested as the N-methyl-D-glucamine salt

5

Example 12 2-(2R-(1R-carboxyethylaminocarbonyl)pyrrolidino-carbonyl)-3-(1-adamantanemethyl(N-methyl)aminocarbonyl)-naphthalene

- 10 The compound was prepared essentially as in example 10 except that the compound of example 9 was used as the acidic substrate instead of the compound of example 3 in step a ¹NMR (d⁶-DMSO) δ 12.8 (1H, s), 8.3-7.5 (7H, m), 4.3-4.1 (2H, m), 3.6-2.7 (6H, m), 2.92 and 2.91 (3H, 2 x s), 2.0 (2H, m), 1.8
- 15 (3H, s), 1.5 (6H, q), 1.4 (6H, m), 1.3 (3H, d).

The material was further characterised and tested as the N-methyl-D-glucamine salt found: C, 53.90; H, 8.28; N, 6.52. C₃₉H₅₆N₄O₁₀. 7.2 H₂O. requires C, 53.82; H, 8.15; N, 6.44%

20

Example 13 2-(2R-(1S-carboxyethylaminocarbonyl)pyrrolidino-carbonyl)-3-(1-adamantanemethyl(N-methyl)aminocarbonyl)-naphthalene

- 25 The compound was prepared essentially as in example 12 except that the PTSA salt of L alanine benzyl ester was used as the basic substrate instead of the PTSA salt of D alanine benzyl ester in step a ¹NMR (d⁶-DMSO) δ 12.8 (1H, s), 8.3-7.5 (7H, m), 4.3-4.1 (2H, m), 3.6-2.7 (6H, m), 2.92 and 2.91
- 30 (3H, 2 x s), 2.0 (2H, m), 1.8 (3H, s), 1.5 (6H, q), 1.4 (6H, m), 1.3 (3H, 2xd).

- The material was further characterised and tested as the N-methyl-D-glucamine salt found: C, 55.36; H, 7.88; N, 6.40.
- 35 C₃₉H₅₆N₄O₁₀. 5.7 H₂O. 0.1 dioxan requires C, 55.52; H, 8.07; N, 6.57%

Example 14 2-(2R-carboxymethylaminocarbonylpyrrolidino-carbonyl)-3-(1-adamantanemethyl(N-methyl)aminocarbonyl)-naphthalene

- 5 The compound was prepared essentially as in example 12 except that the PTSA salt of glycine benzyl ester was used as the basic substrate instead of the PTSA salt of D alanine benzyl ester in step a ¹NMR (d⁶-DMSO) δ 12.7 (1H, s), 8.4-7.5 (7H, m), 4.3-4.1 (1H, m), 3.9-2.7 (8H, m), 2.92 and 2.91
10 (3H, 2 x s), 2.0 (2H, m), 1.8 (3H, s), 1.5 (6H, q), 1.4 (6H, m).

The material was further characterised and tested as the N-methyl-D-glucamine salt found: C, 51.52; H, 7.81; N, 6.29.

- 15 C₃₈H₅₄N₄O₁₀. 8.5 H₂O requires C, 51.84; H, 8.13; N, 6.36%

Example 15 2-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-3-(1-adamantanemethylamino-carbonyl)-naphthalene

20

The compound was prepared essentially as in example 3 except that 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine (prepared as shown below) was used in step a instead of D-proline benzyl ester. ¹NMR (d⁶-DMSO) δ 13.3
25 (2H, s), 10.1 (1H, s), 9.0 (1H, d), 8.7 (3H, m) 8.2 (2H, m), 8.0 (1H, m), 7.9 (1H, m), 7.6 (2H, m), 7.4 (1H, s), 7.3 (5H, m), 4.8 (1H, m), 3.5-2.9 (4H, m), 1.8 (3H, s), 1.5 (6H, q), 1.4 (6H, m).

- 30 The material was further characterised and tested as the di N-methyl-D-glucamine salt found: C, 57.02; H, 7.00; N, 5.63. C₅₄H₇₃N₅O₁₇. 3.7 H₂O. 0.7 dioxan requires C, 57.21; H, 7.27; N, 5.87%

- 35 Preparation of 1S-(3,5-dibenzyloxycarbonylphenylamino-carbonyl)-2-phenylethylamine

a. 3,5-dibenzyloxycarbonyl-nitrobenzene

5-nitro-isophthalic acid (21.1g, 0.1 mol), thionyl chloride (80 ml) and DMF (10 drops) were stirred and heated for about 1h until a clear solution was obtained. Excess thionyl chloride was removed by evaporation and the residual acid chloride was coevaporated with dichloromethane (2 x 100 ml) to remove the last traces.

Benzyl alcohol (21.6 g, 0.2 mol) and triethylamine (30.03 g, 0.3 mol) were dissolved in dichloromethane (200 ml) and stirred at 0° under an atmosphere of dry nitrogen and a solution of the acid chloride in dichloromethane (50 ml) was added dropwise over 20 min. The solution was stirred and refluxed for 1h, and the solution was cooled. The organic layer was washed with water (2 x 100ml), saturated sodium hydrogencarbonate solution (100 ml) and dried over magnesium sulphate. The solution was filtered and evaporated to leave the title compound (39.1g, 100%), ¹H NMR (CDCl₃) δ 9.0 (3H, d), 7.5 (10H, m), 5.5 (4H, s).

20 b. 3,5-dibenzyloxycarbonyl-aniline

3,5-dibenzyloxycarbonyl-nitrobenzene (3.91g, 10 mmol) was dissolved in ethyl acetate (50 ml) and tin(II)chloride dihydrate (11.27g, 50 mmol) was added and the mixture stirred and heated at 70° under an atmosphere of nitrogen for 1h. The mixture was poured carefully onto 5% sodium hydrogencarbonate solution (200 ml) and a further aliquot of ethyl acetate (100 ml) was added. After shaking the organic layer was separated and the aqueous layer was extracted with more ethyl acetate (50 ml). The combined organic layers were washed with brine, and dried, filtered and evaporated to leave a pale yellow solid (3.25g, 90%), ¹H NMR (CDCl₃) δ 8.1 (1H, d), 7.5 (12H, m), 5.4 (4H, s), 3.8 (2H, bs).

35 c. N-tert-butylloxycarbonyl-1S-(3,5-dibenzyloxycarbonyl-phenylaminocarbonyl)-2-phenylethylamine

BOC-L-phenylalanine (8.76 g, 33 mmol) was dissolved in dry

dichloromethane (200 ml) and dry diisopropylethylamine (11.48 ml, 66 mmol) was added followed by PyBROP (15.33g, 33 mmol). The mixture was stirred at room temperature for 5 min and then 3,5-dibenzyloxycarbonyl-aniline (7.22 g, 20 mmol) was added. The solution was stirred at room temperature for a further 5h and the solution was then washed sequentially with 2M hydrochloric acid, water, saturated sodium hydrogencarbonate solution and water and finally dried, filtered and evaporated to leave an oil. This was purified by column chromatography (90% dichloromethane and 10% ethyl acetate) to leave the title compound as a white solid (11.0 g, 90%). ¹H NMR (d⁶-DMSO) δ 10.5 (1H, s), 8.5 (2H, s), 8.2 (1H, s), 7.3 (15H, m), 5.4 (4H, s), 4.3 (1H, m), 2.9 (2H, m), 1.3 (9H, s)

15

d. 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine

N-tert-butyloxycarbonyl-1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine (8.0 g, 13 mmol) was dissolved in trifluoroacetic acid (40 ml) and stirred at room temperature for 30 min. The solvent was removed by evaporation and the residue taken up in dry dichloromethane (50 ml) and basified with diisopropylethylamine. This solution was then used for subsequent transformations.

25

Example 16 2-(2S-(1R-carboxyethylaminocarbonylmethyl)-pyrrolidinocarbonyl)-3-(1-adamantanemethylaminocarbonyl)-naphthalene

30

The compound was prepared essentially as in example 3 except that 2S-(1R-benzyloxycarbonyl-ethylaminocarbonylmethyl)-pyrrolidine in step a instead of D-proline benzyl ester. ¹NMR (d⁶-DMSO) δ 8.5 (1H, m), 8.2 (2H, m), 8.0 (3H, m), 7.6 (2H, m), 4.4-3.9 (2H, m), 3.5-2.7 (8H, m), 2.0 (2H, m), 1.8 (3H, s), 1.5 (6H, q), 1.4 (6H, m), 1.2 (3H, 2 x d).

35

The material was further characterised and tested as the N-

methyl-D-glucamine salt Found: C, 70.34; H, 6.10; N, 5.36.
C₄₂H₄₃N₃O₇. 1.0 methanol requires C, 70.39; H, 6.45; N, 5.73%

Example 17 2-(1S-(3,5-dimethoxycarbonyl-phenylamino-
5 carbonyl)-2-phenylethylaminocarbonyl)-3-(1-adamantane-
methylaminocarbonyl)-naphthalene

The compound of example 15 (479 mg, 0.71 mmol) was dissolved
in methanol (10 ml) and diazomethane solution in diethyl
10 ether (4.74 ml 0.71 mmol) was added dropwise over 5 min. The
solution was evaporated and the crude mixture separated by
column chromatography (silica 7.5% methanol and 92.5%
dichloromethane) to give two products. The less polar
material (r_F 0.8) (70 mg) was the title compound of this
15 example. Found: C, 70.34; H, 6.10; N, 5.36. C₄₂H₄₃N₃O₇. 1.0
methanol requires C, 70.39; H, 6.45; N, 5.73% ¹NMR (d⁶-DMSO)
δ 10.2 (1H, s), 9.0 (1H, d), 8.7 (3H, m) 8.2 (2H, m), 8.0
(1H, m), 7.9 (1H, m), 7.6 (2H, m), 7.4 (1H, s), 7.3 (5H, m),
4.8 (1H, m), 3.9 (6H, s), 3.5-2.9 (4H, m), 1.8 (3H, s), 1.5
20 (6H, q), 1.4 (6H, m).

Example 18 2-(1S-(3-methoxycarbonyl-5-carboxy-
phenylaminocarbonyl)-2-phenylethylaminocarbonyl)-3-(1-
adamantanemethylaminocarbonyl)-naphthalene
25

The more polar material isolated from the chromatography in
example 17 (r_F 0.3) was designated the title compound of
this example. ¹NMR (d⁶-DMSO) δ 10.2 (1H, s), 9.0 (1H, d), 8.7
(1H, s), 8.6 (1H, t), 8.4 (1H, s), 8.2 (2H, m), 8.0 (1H, m),
30 7.9 (1H, m), 7.6 (2H, m), 7.4 (1H, s), 7.3 (5H, m), 4.7 (1H,
m), 3.8 (3H, s), 3.5-2.9 (4H, m), 1.8 (3H, s), 1.5 (6H, q),
1.4 (6H, m).

The material was further characterised and tested as the N-
35 methyl-D-glucamine salt Found: C, 57.31; H, 6.28; N, 4.50.
C₄₈H₅₈N₄O₁₂. 1.8 dicloromethane. 1.9 dioxan requires C, 57.30;
H, 6.43; N, 4.66%

Example 19 (2R-carboxypyrrolidino-carbonyl)-2-(1-adamantanemethylaminocarbonylmethyl)-4,5-dichlorobenzene

a. Preparation of 2-(1-adamantanemethylaminocarbonylmethyl)-
5 4,5-dichlorobenzoic acid

The material was prepared essentially as in example 1 except that 4,5-dichlorophthalic anhydride was used as substrate instead of 2,3-naphthalenedicarboxylic anhydride.

10

b. (2R-carboxypyrrolidino-carbonyl)-2-(1-adamantanemethylaminocarbonylmethyl)-4,5-dichlorobenzene

The material was prepared essentially as in example 3 except
15 that the compound of step a above was used as substrate instead of the compound of example 1 in step a. ¹H NMR (d⁶-DMSO) δ 8.4 (1H, t), 7.9-7.4 (2H, m), 4.2 (1H, m), 3.6-2.7 (6H, m), 2.3 (2H, m), 2.0 (3H, s), 1.7 (6H, q), 1.5 (6H, s).

20

The material was further characterised and tested as the N-methyl-D-glucamine salt found: C, 52.22; H, 7.20; N, 5.87. C₃₁H₄₅Cl₂N₃O₉.2.3 H₂O requires C, 52.03; H, 6.98; N, 5.87%

25 Example 20 1-(1-adamantanemethylaminocarbonyl)-8-naphthoic acid

The material was prepared essentially as in example 1 except that 1,8-naphthalenedicarboxylic anhydride was used as
30 substrate instead of 2,3-naphthalenedicarboxylic anhydride. ¹H NMR (d⁶-DMSO) δ 8.5 (1H, m), 8.4 (1H, t), 8.1-7.5 (5H, m), 2.9 (2H, d), 1.9 (3H, s), 1.6 (6H, m), 1.5 (6H, s).

The material was further characterised and tested as the N-methyl-D-glucamine salt found: C, 62.95; H, 7.26; N, 4.86. C₃₀H₄₂N₂O₈. H₂O requires C, 62.48; H, 7.69; N, 4.86%

Example 21 1/2-(1-adamantanemethylaminocarbonyl)-naphthoic acid Regioisomer 1

The material was prepared essentially as in example 1 except
5 that 1,2-naphthalenedicarboxylic anhydride was used as substrate instead of 2,3-naphthalenedicarboxylic anhydride. Regioisomers were separated by column chromatography (silica 10% methanol and 90% dichloromethane) The less polar compound was designated the compound of this example ¹H NMR
10 (d⁶-DMSO) δ 8.4 (1H, t), 8.1-7.5 (6H, m), 2.9 (2H, d), 1.9 (3H, s), 1.6 (6H, m), 1.5 (6H, s).

The material was further characterised and tested as the N-methyl-D-glucamine salt found: C, 61.82; H, 7.74; N, 5.02.
15 C₃₀H₄₂N₂O₈.1.3 H₂O requires C, 61.96; H, 7.72; N, 4.81%

Example 22 1/2-(1-adamantanemethylaminocarbonyl)-naphthoic acid Regioisomer 2

20 The more polar regioisomer from the chromatography described in example 21 was designated the compound of this example. ¹H NMR (d⁶-DMSO) δ 8.3 (1H, t), 8.1-7.5 (6H, m), 2.9 (2H, d), 1.9 (3H, s), 1.6 (6H, m), 1.5 (6H, s).

25 The material was further characterised and tested as the N-methyl-D-glucamine salt found: C, 60.93; H, 7.81; N, 5.00. C₃₀H₄₂N₂O₈.1.75 H₂O requires C, 61.05; H, 7.77; N, 4.75%

Example 23 2-(1R-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-3-(1-adamantanemethylaminocarbonyl)-naphthalene
30

The compound was prepared essentially as in example 3 except that 1R-(3,5-dibenzoyloxycarbonylphenylaminocarbonyl)-2-phenyl ethylamine was used in step a instead of D-proline
35 benzyl ester. ¹NMR (d⁶-DMSO) δ 13.3 (2H, s), 10.1 (1H, s), 9.0 (1H, d), 8.7 (3H, m) 8.2 (2H, m), 8.0 (1H, m), 7.9 (1H, m), 7.6 (2H, m), 7.4 (1H, s), 7.3 (5H, m), 4.8 (1H, m), 3.5-

2.9 (4H, m), 1.8 (3H, s), 1.5 (6H, q), 1.4 (6H, m).

The material was further characterised and tested as the di N-methyl-D-glucamine salt found: C, 57.02; H, 7.00; N, 5.63.

5 C₅₄H₇₃N₅O₁₇. 3.7 H₂O. 0.7 dioxan requires C, 57.21; H, 7.27; N, 5.87%

Example 24 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylamino-
10 carbonyl)-indole

a. 4-Methyl-5-nitro-phthalic acid

The compound was prepared as in Organic Synthesis collected
15 volume 1, p.408 from 4-methyl phthalic anhydride and fuming nitric acid.

b. Dimethyl 4-methyl-5-nitro-phthalate

20 The compound prepared in step a (4.4 g, 20 mmol) was suspended in methanol (100 ml) and concentrated sulphuric acid (2 ml) and the resulting suspension was heated under reflux for 48h. After cooling dichloromethane (100 ml) was added and the organic layer was washed with saturated sodium
25 hydrogencarbonate solution. The aqueous layer was re-extracted with dichloromethane (100 ml) and the combined organic layers were washed with washed with brine and dried. The solution was filtered and evaporated to yield a white solid which was purified by recrystallisation from hot
30 methanol. The title compound was isolated as white needles (3.14 g, 62%).

c. Dimethyl 4-(2-N,N-dimethylaminoethylene)-5-nitro-phthalate

35

The dimethyl ester prepared in step c above (3.14 g, 12.4 mmol) was dissolved in DMF (10 ml) and dimethylformamide dimethyl acetal (4.43 g, 37.2 mmol) was added. The reaction

mixture was heated at 150° for 6h and then allowed to cool. The solution was diluted with ethyl acetate (500 ml) and the solution was washed with brine (6 x 100 ml), dried filtered and evaporated to leave the title compound as a deep red solid (3.70 g, 97%).

d. 5, 6-Dimethoxycarbonyl-indole

The product of step c (1.50 g) was dissolved in toluene (200 ml) and 10% palladium on charcoal (150 mg) was introduced. The reaction was stirred under an atmosphere of hydrogen at room temperature for 1h. The catalyst was removed by filtration and the solvent by evaporation to leave the title compound (1.14 g).

15

e. Indole-5, 6-dicarboxylic acid

To a stirred solution of the dimethyl ester produced in step d (1.14 g, 4.9 mmol) in a 5:1 mixture of ethanol:water (12 ml) was added solid sodium hydroxide (0.49 g, 12.4 mmol). The solution was stirred at a gentle reflux for 3h. The solution was acidified on cooling to pH2 with hydrochloric acid and then evaporated. The residue was azeotroped with ethanol and then toluene and dried under vacuum. The residue was then extracted with hot acetone (5 x 20 ml) and the combined extracts were evaporated to leave the title compound (870 mg).

25

f. Indole-5, 6-dicarboxylic acid anhydride

30

The product of step e (870 mg) was heated strongly with a heat gun for 10 minutes under vacuum. This left the title compound (800 mg)

g. 6-(1-adamantanemethylaminocarbonyl)-indole-5-carboxylic acid

35

The product of step f (2.61 g, 14 mmol) was dissolved in dry

THF (50 ml) and triethylamine (2.23 ml, 16 mmol) was added followed by 1-adamantanemethylamine (2.5 g, 15.2 mmol). The solution was stirred at room temperature for 1h. The solution was reduced in volume to ca 30 ml and then
5 partitioned between 2M hydrochloric acid (30 ml) and ethyl acetate (30 ml). the organic layer was dried, filtered and evaporated to leave a 3:2 mixture of regioisomers of which the title compound was the major component.

- 10 h. 5-(1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole

The material was made essentially as in example 2 using the
15 mixture of regioisomers isolated in step g above instead of 3-(1-adamantanemethylaminocarbonyl)-2-naphthoic acid and 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine (prepared as shown in example 15) instead of L-alanine methyl ester hydrochloride. This led to a 3:2 mixture of
20 regioisomers which were separated by column chromatography (silica 10% ethyl acetate and 90% dichloromethane to 20% ethyl acetate and 80% dichloromethane). The less polar material was designated the title compound.

- 25 i. 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole

This was prepared essentially as in example 3 step b except that the dibenzyl ester prepared in step h was used as
30 substrate instead of 3-(2R-benzyloxycarbonyl-pyrrolidinocarbonyl)-2-(1-adamantanemethylaminocarbonyl)-naphthalene, ¹H NMR (d⁶-DMSO) δ 11.5 (1H, s), 10.2 (1H, s), 8.7 (1H, d), 8.6 (2H, s), 8.4 (1H, t), 8.2 (1H, s), 7.7 (1H, s), 7.5 (1H, s), 7.2 (6H, m), 6.5 (1H, s), 4.8 (1H, m), 3.5 (1H, m), 3.0
35 (3H, m), 1.8 (3H, s), 1.5 (6H, m), 1.4 (6H, s).

The compound was further characterised and tested as the di-

N-methyl-D-glucamine salt. found: C, 58.05; H, 6.99; N, 7.88. $C_{52}H_{72}N_6O_{17}$, H_2O requires C, 58.31; H, 6.96; N, 7.85%

Example 25 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

a. Benzimidazole-5,6-dicarboxylic acid

10 The compound was prepared from 5,6-dimethylbenzimidazole as described in J.Org.Chem. 1987, 52, 2934.

b. Benzimidazole-5,6-dicarboxylic acid anhydride

15 This was prepared essentially as in example 24 step f except that benzimidazole-5,6-dicarboxylic acid was used as substrate instead of indole-5,6,-dicarboxylic acid.

c. 5-(1-adamantanemethylaminocarbonyl)-benzimidazole-6-
20 carboxylic acid

This was prepared essentially as in example 24 step g except that the product of step b above was used instead of the product of example 24 step f.

25

d. 5-(1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

30 This was prepared essentially as in example 24 step h except that 5-(1-adamantanemethylaminocarbonyl)-benzimidazole-6-carboxylic acid was used as substrate instead of 6-(1-adamantanemethylaminocarbonyl)-indole-5-carboxylic acid and

no separation of regioisomers was required.

e. 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-5 benzimidazole

This was prepared essentially as in example 24 step i except that the dibenzyl ester prepared in step d was used as substrate instead of the product of example 24 step h. ¹H NMR (d⁶-DMSO) δ 10.2 (1H, m), 8.9 (1H, d), 8.7 (2H, s), 8.5 (1H, t), 8.4 (1H, s), 8.2 (1H, m), 7.9 (1H, br s), 7.3 (7H, m), 4.7 (1H, m), 3.5 (1H, m), 3.0 (3H, m), 1.8 (3H, s), 1.5 (6H, m), 1.4 (6H, s).

15 The compound was further characterised and tested as the di-N-methyl-D-glucamine salt. found: C, 55.11; H, 7.09; N, 8.82. C₅₁H₇₁N₇O₁₇. 3.25 H₂O requires C, 55.06; H, 7.02; N, 8.81%

20 Example 26 6-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-5-(1-adamantanemethylaminocarbonyl)-indole

This was prepared essentially as in example 24 except that 25 the more polar dibenzyl ester prepared in step h was used as substrate in step i instead of the product of example 24 step h. ¹H NMR (d⁶-DMSO) δ 11.5 (1H, s), 10.2 (1H, s), 8.8 (1H, d), 8.6 (2H, s), 8.4 (1H, t), 8.2 (1H, s), 7.9 (1H, s), 7.5 (1H, t), 7.2-7.4 (5H, m), 7.0 (1H, s), 6.6 (1H, s), 4.7 (1H, m), 3.4 and 2.9 (4H, m), 1.8 (3H, s), 1.5 (6H, m), 1.3 (6H, s).

Example 27 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-(2-fluorophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole and regioisomer with substituents at 35 positions 5 and 6 reversed

This was prepared essentially as in example 24 except that

1S-(3,5-dibenzyloxycarbonyl-phenylaminocarbonyl)-2-(2-fluorophenyl)ethylamine was used in step h instead of 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine and the mixture of regioisomers formed during this step were not separated. The 1S-(3,5-dibenzyloxy-carbonylphenylaminocarbonyl)-2-(2-fluorophenyl)ethylamine was prepared essentially as in example 15 steps c and d except that BOC-L-2-fluorophenylalanine was used in step c instead of BOC-L-phenylalanine. ¹H NMR (d⁶-DMSO) δ 11.5 (1H, s), 10.3 and 10.2 (1H, 2 x s), 8.8 (1H, m), 8.7 (2H, s), 8.5 (1H, m), 8.2 (1H, s), 7.9 and 7.8 (1H, 2 x s), 7.5-7.0 (6H, m), 6.6 and 6.5 (1H, 2 x s), 4.8 (1H, m), 3.4 and 2.9 (4H, m), 1.8 (3H, s), 1.5 (6H, m), 1.3 (6H, s).

15

The compound was further characterised and tested as the di-N-methyl-D-glucamine salt found: C, 55.28; H, 7.09; N, 7.41. C₅₂H₇₁FN₆O₁₇. 3.33 H₂O requires C, 55.22; H, 6.92; N, 7.43%

20

Example 28 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-(3-fluorophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole and regioisomer with substituents at positions 5 and 6 reversed

25

This was prepared essentially as in example 24 except that 1S-(3,5-dibenzyloxycarbonyl-phenylaminocarbonyl)-2-(3-fluorophenyl)ethylamine was used in step h instead of 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine and the mixture of regioisomers formed during this step were not separated. The 1S-(3,5-dibenzyloxy-carbonylphenylaminocarbonyl)-2-(3-fluorophenyl)ethylamine was prepared essentially as in example 15 steps c and d except that BOC-L-3-fluorophenylalanine was used in step c instead of BOC-L-phenylalanine. ¹H NMR (d⁶-DMSO) δ 11.5 and 11.1 (1H, 2 x s), 10.3 and 10.2 (1H, 2 x s), 8.8 (1H, m), 8.7 (2H, s), 8.4 (1H, m), 8.2 (1H, s), 7.9 and 7.7 (1H, 2 x s), 7.5-7.0 (6H,

m), 6.6 and 6.5 (1H, 2 x s), 4.8 (1H, m), 3.4 and 2.9 (4H, m), 2.0 and 1.8 (3H, m), 1.5 (6H, m), 1.3 (6H, s).

The compound was further characterised and tested as the di-
5 N-methyl-D-glucamine salt found: C, 55.80; H, 6.84; N, 7.25.
C₅₂H₇₁FN₆O₁₇. 2.9 H₂O requires C, 55.59; H, 6.89; N, 7.48%

Example 29 5-(1R-(3,5-dicarboxyphenylaminocarbonyl)-2-
10 phenylethylaminocarbonyl)-6-(1-adamantanemethylamino-
carbonyl)-indole and regioisomer with substituents at
positions 5 and 6 reversed

This was prepared essentially as in example 24 except that
15 1R-(3,5-dibenzyloxycarbonyl-phenylaminocarbonyl)-2-
phenylethy lamine was used in step h instead of 1S-(3,5-
dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethyl amine
and the mixture of regioisomers formed during this step were
not separated. The 1R-(3,5-dibenzyloxy-carbonylphenylamino-
20 carbonyl)-2-phenylethylamine was prepared essentially as in
example 15 steps c and d except that BOC-D-phenylalanine was
used in step c instead of BOC-L-phenylalanine. ¹H NMR (d⁶-
DMSO) δ 11.5 (1H, s), 10.3 and 10.2 (1H, 2 x s), 8.8 (1H,
m), 8.7 (2H, s), 8.4 (1H, m), 8.2 (1H, s), 7.9 and 7.7 (1H,
25 2 x s), 7.5-7.0 (7H, m), 6.6 and 6.5 (1H, 2 x s), 4.7 (1H,
m), 3.4 and 2.9 (4H, m), 1.8 (3H, m), 1.5 (6H, m), 1.3 (6H,
s).

The compound was further characterised and tested as the di-
30 N-methyl-D-glucamine salt found: C, 55.51; H, 7.29; N, 7.34.
C₅₂H₇₂N₆O₁₇. 4.1 H₂O requires C, 55.44; H, 7.17; N, 7.46%

Example 30 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-(4-
hydroxyphenyl)e thylaminocarbonyl)-6-(1-adamantanemethyl-
35 aminocarbonyl)-indole and regioisomer with substituents at
positions 5 and 6 reversed

This was prepared essentially as in example 24 except that

- 1S-(3,5-dibenzyloxycarbonyl-phenylaminocarbonyl)-2-(4-hydroxy phenyl)ethylamine was used in step h instead of 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine and the mixture of regioisomers formed during this step were not separated. The 1S-(3,5-dibenzyloxy-carbonylphenylaminocarbonyl)-2-(4-hydroxy phenyl)ethylamine was prepared essentially as in example 15 steps c and d except that BOC-L-tyrosine(O-benzyl ether) was used in step c instead of BOC-L-phenylalanine and pentamethylbenzene and trifluoroacetic acid were used together to remove both the BOC group and the tyrosinyl benzyl protection during the course of step d. ¹H NMR (d⁶-DMSO) δ 11.5 and 11.4 (1H, 2 x s), 10.3 and 10.2 (1H, 2 x s), 9.2 (1H, br s), 8.8 (1H, m), 8.7 (2H, s), 8.4 (1H, m), 8.2 (1H, s), 7.9 and 7.7 (1H, 2 x s), 7.5 (1H, m), 7.2 (3H, m), 6.7 (2H, m), 6.6 and 6.5 (1H, 2 x s), 4.6 (1H, m), 3.4 and 2.9 (4H, m), 2.0 and 1.8 (3H, m), 1.6 (6H, m), 1.4 (6H, s).
- 20 The compound was further characterised and tested as the di-N-methyl-D-glucamine salt found: C, 53.41; H, 6.95; N, 6.85. C₅₂H₇₂N₆O₁₈. 5.9 H₂O requires C, 53.13; H, 7.19; N, 7.15%
- 25 Example 31 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-(4-aminophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole and regioisomer with substituents at positions 5 and 6 reversed
- 30 This was prepared essentially as in example 24 except that 1S-(3,5-dibenzyloxycarbonyl-phenylaminocarbonyl)-2-(4-nitroph enyl)ethylamine was used in step h instead of 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine and the mixture of regioisomers formed during this step were not separated. The nitro group was reduced to the amino group during the final deprotection step. The 1S-(3,5-dibenzyloxy-carbonylphenylaminocarbonyl)-2-(4-nitrophenyl)ethylamine was prepared essentially as in

example 15 steps c and d except that BOC-L-4-nitrophenylalanine was used in step c instead of BOC-L-phenylalanine. ¹H NMR (d⁶-DMSO) δ 11.5 (1H, 2 x s), 10.2 and 10.1 (1H, 2 x s), 8.8 (1H, m), 8.7 (2H, s), 8.4 (1H, m), 8.2
5 (1H, s), 7.9 and 7.7 (1H, 2 x s), 7.5-7.0 (4H, m), 6.5 (3H, 2 x s), 4.6 (1H, m), 3.2 and 2.8 (4H, m), 1.8 (3H, m), 1.5 (6H, m), 1.4 (6H, s).

The compound was further characterised and tested as the
10 mono-N-methyl-D-glucamine salt found: C, 58.32; H, 6.73; N, 9.00. C₄₅H₅₆FN₆O₁₂. 3.0 H₂O requires C, 58.30; H, 6.74; N, 9.06%

15 Example 32 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-(4-iodophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole

a. 3,5-di-t-butyloxycarbonyl-nitrobenzene

20

5-Nitroisophthalic acid (4.22 g, 20 mmol) was suspended in dichloromethane (80 ml) and concentrated sulphuric acid (1 ml) was added. The solution was stirred and then saturated with isobutylene gas. The reaction vessel was stoppered and
25 stirred at room temperature overnight. The solution was filtered and anhydrous potassium carbonate was added to the filtrate. the solution was filtered and evsaporated and the residue recrystallised from ethanol to leave the title compound as a white solid (2.2 g).

30

b. 3,5-di-t-butyloxycarbonyl-aniline

The nitro compound prepared in step a (2.2 g, 6.8 mmol) was dissolved in a mixture of THF (50 ml) and methanol (50 ml)
35 and 10% palladium on charcoal (100 mg) was added. The reaction mixture was stirred under an atmosphere of hydrogen overnight. The catalyst was removed by filtration and the title compound (1.94 g) isolated by evaporation.

c. N-(9-fluorenylmethoxycarbonyl)-1S-(3,5-di-t-butyloxy-carbonylphenylaminocarbonyl)-2-(4-iodophenyl)ethylamine

FMOC-L-4-iodophenylalanine (3.85 g, 7.5 mmol) and PyBROP
5 (3.5 g, 7.5 mmol) were stirred in a mixture of dichloromethane (25 ml) and diisopropylethylamine (2.63 ml, 15 mmol) for 5 min. A solution of 3,5-di-t-butyloxycarbonyl-aniline (1.94 g, 6.6 mmol) in dichloromethane (15 ml) was added followed by DMAP (5 mg). The resulting solution was
10 stirred at room temperature overnight. The solution was washed with 2M hydrochloric acid (2 x 25 ml) and brine (25 ml) dried filtered and evaporated. The residue was recrystallised from ethanol to leave the title compound as a white solid (1.91 g).

15

d. S-(3,5-di-t-butyloxycarbonylphenylaminocarbonyl)-2-(4-iodophenyl)ethylamine

The FMOC derivative produced in step c (1.7 g) was dissolved
20 in diethylamine (20 ml) and stirred at room temperature for 2h. The solution was evaporated and then the residue was purified by column chromatography (silica 50% dichloromethane and 50% ethyl acetate) to leave the title compound.

25 e. 5-(1S-(3,5-di-t-butyloxycarbonylphenylaminocarbonyl)-2-(4-iodophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole

The product of step d (220 mg, 0.35 mmol) and the product of
30 example 24 step g (73 mg, 0.35 mmol) were dissolved in dry DMF (3 ml) and DCCI (73 mg, 0.35 mmol), HOBT (50 mg, 0.35 mmol) and DMAP (5 mg) were added. The solution was stirred at room temperature for 4h. The DCU produced was removed by filtration and washed with dichloromethane. The filtrate was
35 further diluted with dichloromethane and then washed with 2M hydrochloric acid (2 x 10 ml), brine (10 ml) and water (10 ml) before being dried (magnesium sulphate) and evaporated to leave a mixture of regioisomers at positions 5 and 6 of

the indole ring. The regioisomers were separated by column chromatography (silica 80% dichloromethane and 20% ethyl acetate) to leave the less polar material as title compound (55 mg).

5

f. 5-(1S-(3,5-di-carboxyphenylaminocarbonyl)-2-(4-iodophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole

- 10 The product of step e (50 mg) was dissolved in TFA (1ml) and stirred at room temperature for 1h. The solution was filtered and evaporated and the residue co-evaporated several times with diethyl ether. The residue was triturated with ether and the solid filtered off and dried. The title
- 15 compound was left as a white solid. ¹H NMR (d⁶-DMSO) δ 11.5 (1H, s), 10.7 (1H, s), 8.8 (1H, d), 8.5 (1H, m), 8.4 (2H, s), 8.2 (1H, s), 7.7 (3H, s), 7.5 (2H, m), 7.2 (2H, m), 7.0 (1H, s), 6.5 (1H, s), 4.7 (1H, m), 3.4 and 2.9 (4H, m), 1.9 (3H, s), 1.5 (6H, m), 1.3 (6H, s).

20

Example 33 5-(1S-(3,5-dipivaloyloxymethyloxycarbonyl-phenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole

25

- The compound of example 24 (331 mg, 0.5 mmol) was dissolved in DMF (2.5 ml) and cesium carbonate (168 mg, 0.5 mmol) and pivaloyloxymethyl chloride (0.144 ml, 1.0 mmol) were added. After 30 min at room temperature the reaction mixture was
- 30 partitioned between ethyl acetate (30 ml) and 2M hydrochloric acid (30 ml). The organic layer was washed with water (3 x 20 ml), dried (magnesium sulphate) and evaporated to leave a white foam which was purified by column chromatography (silica 80% dichloromethane and 20% ethyl
- 35 acetate) to leave the title compound, found: C, 67.29; H, 6.61; N, 6.28. C₅₀H₅₈N₄O₁₁ requires C, 67.40; H, 6.56; N, 6.29%, ¹H NMR (d⁶-DMSO) δ 11.5 (1H, s), 10.3 (1H, s), 8.8 (3H, m), 8.5 (1H, t), 8.2 (1H, s), 7.7 (1H, s), 7.5 (1H, t),

7.2-7.5 (5H, m), 7.2 (1H, s), 6.5 (1H, s), 6.0 (4H, m), 4.7 (1H, m), 3.4 and 2.9 (4H, m), 1.8 (3H, s), 1.3-1.6 (12H, m), 1.1 (18H, s).

5

Example 34 5-(1S-(3,5-dihydroxyaminocarbonylphenylamino-carbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole

- 10 The compound of example 24 (300 mg, 0.45 mmol) was dissolved in DMF (5 ml). Pentafluorophenol (184 mg, 1.0 mmol) and DCCI (206 mg, 1.0 mmol) were introduced and the mixture stirred at room temperature for 3h. The solution was filtered and hydroxylamine hydrochloride (100 mg, 1.4 mmol) and
15 triethylamine (0.2 ml) was added. The solution was stirred overnight and then evaporated. The material left was partitioned between ethyl acetate and 2M hydrochloric acid. The organic layer was dried, filtered and evaporated to leave a solid which was triturated with several portions of
20 diethyl ether. The white solid left by this procedure was isolated by filtration and dried. This was then recrystallised from a 1:1 mixture of hexane and ethyl acetate to leave the title compound (110 mg). ¹H NMR (d⁶-DMSO) δ 11.6 (1H, s), 11.2 (2H, br s), 10.2 (1H, s), 8.8
25 (1H, d), 8.5 (3H, m), 8.0-7.1 (9H, m), 6.5 (1H, s), 4.7 (1H, m), 3.4 and 2.9 (4H, m), 1.8 (3H, s), 1.6 (6H, m), 1.3 (6H, s).

- Example 35 5-(1S-(3,5-dimethoxycarbonylphenylamino-carbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole
30

- The compound of example 24 (155 mg, 0.23 mmol) was dissolved in methanol (5 ml). A 2M hexane solution of trimethylsilyl-
35 diazomethane in hexane (1 ml) was added and left to stir for 30 min. The yellow solution was evaporated and the residue partitioned between ethyl acetate and water. The aqueous phase was extracted with ethyl acetate and the combined

organic extracts were dried (magnesium sulphate), filtered and evaporated. The residue was recrystallised from methanol to leave the title compound found: C, 66.00; H, 6.10; N, 7.91. $C_{40}H_{42}N_4O_7 \cdot 1.9 H_2O$ requires C, 66.27; H, 6.37; N, 7.73%, 1H NMR ($CDCl_3$) δ 9.9 (1H, d), 9.2 (1H, s), 8.7 (2H, d), 8.4 (1H, t), 7.5 (1H, s), 7.3 (7H, s), 6.7 (1H, s), 6.4 (2H, m), 5.0 (1H, m), 3.9 (6H, s), 3.4 and 2.9 (4H, m), 1.9 (3H, s), 1.6 (6H, m), 1.4 (6H, s).

10 Example 36 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-N-methyl-indole

a. 5-(1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-N-methyl-indole

5-(1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole, the title compound of Example 24 step h. (211mg, 0.25 mmol) was dissolved in dry THF (1 ml) and dry DMF (0.5 ml). The reaction mixture was stirred under an atmosphere of dry nitrogen and sodium hydride (15 mg, 0.3 mmol) was added. Hydrogen gas was evolved for about 5 min and then methyl iodide (0.04 ml) was added. The mixture was stirred at room temperature for 1h, diluted with brine (20 ml) and extracted with dichloromethane (20 ml). The organic layer was washed with brine (2 x 20 ml), dried (magnesium sulphate), and evaporated. The residue was purified by column chromatography (silica 85% dichloromethane and 15% ethyl acetate) to leave the title compound (90 mg).

b. 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-N-methyl-indole

This was prepared essentially as in example 3 step b except that the product of step a above was used as substrate

instead of 3-(2R-benzyloxycarbonyl-pyrrolidino-carbonyl)-2-(1-adamantane methylaminocarbonyl)-naphthalene. ¹H NMR (d⁶-DMSO) δ 10.2 (1H, s), 8.8 (1H, d), 8.7 (2H, s), 8.4 (1H, t), 8.2 (1H, s), 7.7 (1H, s), 7.5 (1H, d), 7.2-7.4 (5H, m), 7.1
5 (1H, s), 6.5 (1H, d), 4.7 (1H, m), 3.8 (3H, s), 3.4 and 2.9 (4H, m), 1.8 (3H, s), 1.5 (6H, m), 1.4 (6H, s).

The compound was further characterised and tested as the di-N-methyl-D-glucamine salt found: C, 59.47; H, 7.24; N, 7.79.
10 C₅₃H₇₄N₆O₁₇ requires C, 59.65; H, 6.99; N, 7.88%

Example 37 6-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-5-(1-adamantanemethylaminocarbonyl)-N-methyl-indole

15

This was prepared essentially as in example 36 except that the more polar dibenzyl ester prepared in example 24 step h was used as substrate in step a instead of 5-(1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole ¹H NMR
20 (d⁶-DMSO) δ 10.2 (1H, s), 8.7 (2H, m), 8.4 (1H, t), 8.2 (1H, s), 7.9 (1H, s), 7.5 (1H, d), 7.2-7.4 (5H, m), 6.8 (1H, s), 6.6 (1H, d), 4.7 (1H, m), 3.8 (3H, s), 3.4 and 2.9 (4H, m), 1.8 (3H, s), 1.5 (6H, m), 1.4 (6H, s).

25

The compound was further characterised and tested as the di-N-methyl-D-glucamine salt found: C, 56.77; H, 7.22; N, 7.61. C₅₃H₇₄N₆O₁₇ . 3H₂O requires C, 56.77; H, 7.19; N, 7.50%

30 Example 38 5-(1S-(3,5-methoxyaminocarbonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole and regioisomer with substituents at positions 5 and 6 reversed

35 The compound was prepared essentially as in example 24 except that 1S-(3,5-dimethoxycarbonylphenylaminocarbonyl)-2-phenylethylamine was used in step h instead of 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine,

DCCI/HOBT coupling conditions were used and the mixture of regioisomers formed during this step were not separated. The 1S-(3,5-dimethoxycarbonylphenylaminocarbonyl)-2-phenylethylamine was prepared by hydrogenation of the product of
5 example 15 steps c followed treatment of the resulting diacid with O-methyl-hydroxamic acid hydrochloride in the presence of PyBROP and diisopropylethylamine. found: C, 61.86; H, 6.70; N, 10.83. $C_{40}H_{44}N_6O_7 \cdot 3.15 H_2O$ requires C, 61.79; H, 6.52; N, 10.81% 1H NMR (d^6 -DMSO) δ 11.8 (2H, br s),
10 11.5 (1H, s), 10.3 and 10.2 (1H, 2 x s), 8.8 (1H, m), 8.5 (3H, m), 8.0-7.1 (9H, m), 6.5 (1H, m), 4.7 (1H, m), 3.7 (6H, 2 x s), 3.6 - 2.7 (4H, m), 1.8 (3H, s), 1.5 (6H, m), 1.4 (6H, s).

15 Example 39 5-(1S-(3-methoxycarbonyl-5-pivaloyloxymethyloxycarbonyl-phenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole and regioisomer with substituents at positions 5 and 6 reversed

20 The compound was prepared essentially as in example 38 except that 1S-(3-methoxycarbonyl-5-pivaloyloxymethyloxycarbonyl-phenylaminocarbonyl)-2-phenylethylamine was used in step h instead of 1S-(3,5-dimethoxycarbonylphenylaminocarbonyl)-2-phenylethylamine.
25 1S-(3-methoxycarbonyl-5-pivaloyloxymethyloxycarbonyl-phenylaminocarbonyl)-2-phenylethylamine was prepared essentially as in example 15 step c except that 3-methoxycarbonyl-5-pivaloyloxymethyloxycarbonyl-aniline was used as substrate instead of 3,5-dibenzyloxycarbonylaniline.
30 This in turn was prepared by the treatment of monomethyl-5-nitroisophthalate with cesium carbonate and chloromethyl-pivalate followed by catalytic hydrogenation, found: C, 68.01; H, 6.42; N, 6.84. $C_{45}H_{50}N_4O_9$ requires C, 68.34; H, 6.37; N, 7.08% 1H NMR (d^6 -DMSO) δ 11.5 (1H, s), 10.3 and 10.2
35 (1H, 2 x s), 8.8 (3H, m), 8.5 (1H, m), 8.2 (1H, s), 7.9 and 7.7 (1H, 2 x s), 7.5-7.0 (7H, m), 6.5 (1H, m), 5.9 (2H, s), 4.7 (1H, m), 3.9 (3H, s), 3.4 and 2.7 (4H, m), 1.8 (3H, s), 1.5 (6H, m), 1.4 (6H, s), 1.1 (9H, s).

Example 40 5-(1S-(3-methoxycarbonyl-5-carboxy-phenylamino-carbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole and regioisomer with substituents at positions 5 and 6 reversed

5

The compound of example 39 (300 mg) was treated with a saturated solution of ammonia in methanol (20 ml). The solution was stirred for 1h and on evaporation the residue was purified by column chromatography (silica 95%
10 dichloromethane and 5% methanol) to leave the title compound (52 mg), ¹H NMR (d⁶-DMSO) δ 11.5 (1H, s), 10.3 and 10.2 (1H, 2 x s), 8.8 (1H, m), 8.6 (2H, m), 8.5 (1H, m), 8.2 (1H, s), 7.9 and 7.7 (1H, 2 x s), 7.5-7.0 (7H, m), 6.7 (1H, s), 4.7 (1H, m), 3.8 (3H, s), 3.4 and 2.7 (4H, m), 1.8 (3H, s), 1.5
15 (6H, m), 1.4 (6H, s).

The compound was further characterised and tested as the N-methyl-D-glucamine salt found: C, 60.71; H, 6.96; N, 7.89. C₄₆H₅₇N₅O₁₂ .2H₂O requires C, 60.85; H, 6.77; N, 7.71%

20

Example 41 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethyl-N-methylaminocarbonyl)-indole and regioisomer with substituents at positions 5 and 6 reversed

25

The material was prepared essentially as in example 24 except that N-methyl-1-adamantanemethylamine was used in step g instead of 1-adamantanemethylamine and that the regioisomers were not separated at the end of step h, ¹H NMR
30 (d⁶-DMSO) δ 11.5 and 11.3 (1H, 2 x s), 10.3 and 10.2 (1H, 2 x s), 8.7 (1H, m), 8.6 (2H, m), 8.5 (1H, m), 8.2 (1H, s), 7.9 and 7.8 (1H, 2 x s), 7.5-7.0 (7H, m), 6.5 (1H, m), 4.7 (1H, m), 3.2 (4H, m), 2.7 (3H, m), 1.8 (3H, s), 1.5 (12H, m).

35

The compound was further characterised and tested as the di-N-methyl-D-glucamine salt found: C, 59.76; H, 7.04; N, 7.68. C₅₃H₇₄N₆O₁₇ requires C, 59.65; H, 6.99; N, 7.88%

Example 42 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(cycloheptanemethylaminocarbonyl)-indole and regioisomer with substituents at positions 5 and 6 reversed

5

The material was prepared essentially as in example 24 except that cycloheptanemethylamine was used in step g instead of 1-adamantanemethylamine and that the regioisomers were not separated at the end of step h, ^1H NMR (d^6 -DMSO) δ

10 11.5 (1H, s), 10.3 and 10.2 (1H, 2 x s), 8.7 (3H, m), 8.5 (1H, m), 8.2 (1H, s), 7.8 and 7.6 (1H, 2 x s), 7.5-7.0 (7H, m), 6.5 (1H, m), 4.7 (1H, m), 3.2-2.7 (4H, m), 1.7-1.0 (13H, m).

15 The compound was further characterised and tested as the di-N-methyl-D-glucamine salt found: C, 54.09; H, 7.17; N, 7.41. $\text{C}_{49}\text{H}_{70}\text{N}_6\text{O}_{17} \cdot 4.3\text{H}_2\text{O}$ requires C, 53.85; H, 7.25; N, 7.69%

Example 43 5-(1S-(3,5-diaminophenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethyl-N-methylaminocarbonyl)-indole and regioisomer with substituents at positions 5 and 6 reversed

20

a. N-tert-butyloxycarbonyl-1S-(3,5-dinitrophenylaminocarbonyl)-2-phenylethylamine

25

3,5-Dinitroaniline (3.44g, 18.7 mmol) and BOC-L-phenylalanine methyl ester (5.24 g, 18.7 mmol) were dissolved in 1,2-dichloroethane (50 ml) and cooled to -10° .

30 Trimethylaluminium (3.6 ml, 37.4 mmol) was added and the mixture was allowed to warm to room temperature and stirred for 10d. 2M sodium hydroxide solution (20 ml) was added and the reaction mixture filtered through celite, washed with brine and treated with three aliquots of magnesium sulphate,

35 charcoal and celite. After evaporation, the residual material was chromatographed (silica gradient 5-10% ethyl acetate and dichloromethane) and recrystallised from a mixture of dichloromethane and hexane to leave the title

compound as a pale yellow solid (2.99g).

- b. 5-(1S-(3,5-diaminophenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethyl-N-methylaminocarbonyl)-indole and regioisomer with substituents at positions 5 and 6 reversed

The material was prepared essentially as in example 24 except that the product of step a above was used in step h after the BOC group had been removed with trifluoroacetic acid, instead of 1S-(3,5-dibenzoyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine and the mixture of regioisomers formed during this step were not separated. The amine groups were formed by the final hydrogenation step, ¹H NMR (d⁶-DMSO) δ 11.5 (1H, 2 x s), 9.4 (1H, d), 8.5 (1H, dd), 8.3 (1H, m), 7.8-6.5 (9H, m), 6.4 (2H, dd), 5.6 (1H, d), 4.7 (1H, m), 4.6 4H, br s), 3.0-2.8 (4H, m), 2.7 (3H, m), 1.9 (3H, m), 1.6 (6H, m), 1.5 (6H, m).

- 20 The compound was further characterised and tested as the dihydrochloride salt found: C, 54.90; H, 6.63; N, 10.88. C₃₆H₄₂Cl₂N₆O₃ .6H₂O requires C, 55.18; H, 6.92; N, 10.73%

- Example 44 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-N-acetyl-indole

- The unseparated mixture of diastereomers isolated at the end of example 24 step h (251 mg, 0.3 mmol) was dissolved in DMF (0.5 ml) and 60% sodium hydride (14 mg, 0.36 mmol) was added. This was accompanied with effervescence. To the yellow solution was added acetyl chloride (0.026 ml, 0.36 mmol) and the mixture was stirred for 2h at RT. A few drops of water were introduced before the whole reaction mixture was poured into water (0.5 ml). The aqueous mixture was extracted with diethyl ether (5 x 5ml) and the combined organic layers dried (magnesium sulphate). The product was finally purified by column chromatography (silica 10% ethyl

acetate and 90% dichloromethane) to leave the dibenzyl ester of the title compound (92 mg). This was converted to the title compound by hydrogenation essentially as described in example 3 step b. ¹H NMR (d⁶-DMSO) δ 13.3 (2H, br s), 10.2 (1H, 2 x s), 8.9 (1H, m), 8.6 (3H, m), 8.1 (1H, s), 8.1-7.9 (2H, m), 7.4-7.1 (6H, m), 6.8 (1H, m), 4.7 (1H, m), 3.4-2.9 (4H, m), 2.7 (3H, 2 x s), 1.9 (3H, m), 1.6 (6H, m), 1.5 (6H, m).

- 10 The compound was further characterised and tested as the di-N-methyl-D-glucamine salt found: C, 56.96; H, 7.11; N, 7.44. C₅₄H₇₄N₆O₁₈ .2.6H₂O requires C, 56.79; H, 6.99; N, 7.36%

- Example 45 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylamino-carbonyl)-N-phenylsulphonyl-indole

- The material was prepared essentially as in example 44 except that phenylsulphonyl chloride was used instead of acetyl choride, ¹H NMR (d⁶-DMSO) δ 13.3 (2H, br s), 10.1 (1H, 2 x s), 9.2 and 8.9 (1H, 2 x d), 8.7-8.6 (3H, m), 8.2 (2H, s), 8.0 (2H, m), 7.9-7.1 (10H, m), 6.9 (1H, m), 4.7 (1H, m), 3.5-2.9 (4H, m), 1.9 (3H, m), 1.6 (6H, m), 1.5 (6H, m).

- 25 The compound was further characterised and tested as the di-N-methyl-D-glucamine salt found: C, 55.23; H, 6.88; N, 6.72. C₅₈H₇₆N₆O₁₉S.4.0H₂O requires C, 56.07; H, 6.69; N, 6.64%

- Example 46 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(2,2-dimethylpropylamino-carbonyl)-indole and regioisomer with substituents at positions 5 and 6 reversed

- The material was prepared essentially as in example 24 except that 2,2-dimethyl-propylamine was used in step g instead of 1-adamantanemethylamine and that the regioisomers were not separated at the end of step h, ¹H NMR (d⁶-DMSO) δ 11.5 (1H, s), 10.3 and 10.2 (1H, 2 x s), 8.7 (3H, m), 8.5

(1H, m), 8.2 (1H, s), 7.8 and 7.7 (1H, 2 x s), 7.5-7.0 (7H, m), 6.5 (1H, m), 4.7 (1H, m), 3.2-2.9 (4H, m), 0.8 (9H, s).

The compound was further characterised and tested as the di-
5 N-methyl-D-glucamine salt found: C, 53.21; H, 7.12; N, 8.08.
C₄₆H₆₆N₆O₁₇ .3.5H₂O requires C, 53.19; H, 7.09; N, 8.09%

Example 47 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-
phenylethylaminocarbonyl)-6-(1-adamantanemethylamino-
10 carbonyl)-indole

The material was prepared essentially as in example 24
except that 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-
ethylamine was used in step h instead of 1S-(3,5-dibenzyl-
15 oxycarbonylphenylaminocarbonyl)-2-phenylethylamine. The less
polar regioisomer after this step was taken through to the
title compound by hydrogenation. The 1S-(3,5-
dibenzyloxycarbonylphenylaminocarbonyl)-ethylamine was
prepared essentially as in example 15 steps c and d except
20 that BOC-L-alanine was used in step c instead of BOC-L-
phenylalanine. ¹H NMR (d⁶-DMSO) δ 11.5 (1H, s), 10.1 (1H, s),
8.7 (3H, m), 8.5 (1H, m), 8.2 (1H, s), 7.7 (1H, s), 7.6 (1H,
s), 7.5 (1H, s), 6.5 (1H, s), 4.5 (1H, m), 2.9 (2H, m), 1.8
(3H, s), 1.5 (15H, m).

25

The compound was further characterised and tested as the di-
N-methyl-D-glucamine salt found: C, 53.04; H, 7.26; N, 8.05.
C₄₆H₆₈N₆O₁₇ .3.6H₂O requires C, 53.05; H, 7.27; N, 8.06%

30 Example 48 6-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-
phenylethylaminocarbonyl)-5-(1-adamantanemethylamino-
carbonyl)-indole

The material was prepared essentially as in example 47
35 except that the more polar regioisomer after this step was
taken through to the title compound by hydrogenation, ¹H NMR
(d⁶-DMSO) δ 11.5 (1H, s), 10.2 (1H, s), 8.7 (3H, m), 8.4
(1H, m), 8.2 (1H, s), 7.9 (1H, s), 7.5 (2H, m), 6.6 (1H, s),

4.5 (1H, m), 2.9 (2H, m), 1.8 (3H, s), 1.5 (15H, m).

The compound was further characterised and tested as the di-N-methyl-D-glucamine salt found: C, 56.32; H, 7.27; N, 8.42.

5 C₄₆H₆₈N₆O₁₇ requires C, 56.55; H, 7.02; N, 8.60%

Example 49 5-(1S-(trans 3,4-dimethoxycarbonylpyrrolidinocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole and regioisomer with substituents at
10 positions 5 and 6 reversed

The material was prepared essentially as in example 24 except that 1S-(trans 3,4-dimethoxycarbonylpyrrolidinocarbonyl)-2-phenylethylamine was used in
15 step h instead of 1S-(3,5-dibenzoyloxycarbonylphenylaminocarbonyl)-2-phenylethyl amine. The mixture of regioisomers was not separated and no hydrogenation was performed as a final step as no deprotection was required. ¹H NMR (d⁶-DMSO) δ 11.4 (1H, m), 9.9 (0.5H, m), 8.6 (0.5H, m), 8.2 (1H, m),
20 7.7-7.1 (8H, m), 6.5 (1H, m), 4.8 and 4.6 (1H, 2 x m), 3.6 (6H s), 3.2 -2.9 (8H, m), 1.9 (3H, s), 1.8 (2H, t), 1.5 (6H, m), 1.4 (6H, m).

Example 50 5-(1S-(trans 3,4-dicarboxypyrrolidinocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole and regioisomer with substituents at
25 positions 5 and 6 reversed

The material of example 49 (200 mg, 0.3 mmol) was dissolved
30 in a 1:1 mixture of methanol and water (10 ml) and lithium hydroxide (28 mg, 0.6 mmol) was added. The temperature of the reaction vessel was raised to 80° for two minutes and on cooling the reaction mixture was evaporated and acidified to pH3 with 2M hydrochloric acid. The precipitated material was
35 filtered and dried to leave the title compound (44 mg), ¹H NMR (d⁶-DMSO) δ 12.7 (2H, br s), 11.4 (1H, m), 8.6 (1H, m), 8.2 (1H, m), 7.7-7.1 (8H, m), 6.5 (1H, m), 4.8 (1H, m), 3.2 -2.9 (8H, m), 1.9 (5H, m), 1.5 (6H, m), 1.4 (6H, s).

The compound was further characterised and tested as the di-N-methyl-D-glucamine salt found: C, 58.27; H, 7.38; N, 8.06. $C_{50}H_{74}N_6O_{17}$ requires C, 58.24; H, 7.23; N, 8.15%

5 Example 51 3-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-2-(1-adamantanemethylamino-carbonyl)-carbazole

This was prepared essentially as in example 24 except that
10 the dimethyl ester of carbazole-2,3-dicarboxylic acid was used in step e instead of the dimethyl ester of indole-5,6-dicarboxylic acid. The carbazole substrate was made as in J.Chem.Res, 1990, 1919. 1H NMR (d^6 -DMSO) δ 13.2 (2H, br s), 11.6 (1H, s), 10.2 (1H, s), 8.8 (1H, d), 8.7 (2H, s), 8.6
15 (1H, t), 8.2 (1H, s), 8.0 (1H, d), 7.7 (1H, s), 7.6 (1H, t), 7.5-7.3 (7H, m), 7.2 (1H, t), 4.8 (1H, m), 3.4 and 3.0 (4H, m), 1.9 (3H, s), 1.5 (6H, m), 1.4 (6H, s).

Example 52 2-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-3-(1-adamantanemethylamino-carbonyl)-carbazole
20

This was prepared essentially as in example 26 except that the dimethyl ester of carbazole-2,3-dicarboxylic acid was
25 used in step e instead of the dimethyl ester of indole-5,6-dicarboxylic acid. The carbazole substrate was made as in J.Chem.Res, 1990, 1919. 1H NMR (d^6 -DMSO) δ 11.7 (1H, s), 10.3 (1H, s), 9.0 (1H, d), 8.7 (2H, s), 8.5 (1H, t), 8.2 (1H, m), 7.9 (1H, s), 7.6-7.3 (8H, m), 7.0 (1H, s), 4.8 (1H, m), 2.8
30 and 2.5 (4H, m), 1.9 (3H, s), 1.5 (6H, m), 1.3 (6H, s).

Example 53 3-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-2-(1-adamantanemethylamino-carbonyl)-5,7-diacetoxy-naphthalene, arbitrary assignment of
35 regioisomers at positions 2 and 3.

This was prepared essentially as in example 24 except that 5,7-diacetoxy-naphthalene-2,3-dicarboxylic acid anhydride

was used in step f instead of indole-5,6-dicarboxylic acid anhydride. The naphthalene substrate was made in several steps from naphthalene-2,3-dicarboxylic acid. ¹H NMR (d⁶-acetone) δ 10.2 (1H, s), 9.0 (2H, s), 8.6-8.1 (3H, m), 7.6-7.1 (9H, m), 5.0 (1H, m), 3.2 (4H, m), 2.4 (6H, dd), 1.8 (3H, s), 1.6 (12H, m).

The compound was further characterised and tested as the di-N-methyl-D-glucamine salt found: C, 55.31; H, 6.62; N, 5.64.

10 C₅₈H₇₇N₅O₂₁ .4.1 H₂O requires C, 55.54; H, 6.85; N, 5.58%

Example 54 2-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-3-(1-adamantanemethylaminocarbonyl)-5,7-diacetoxy-naphthalene, arbitrary assignment of regioisomers at positions 2 and 3.

15

This was prepared essentially as in example 26 except that 5,7-diacetoxy-naphthalene-2,3-dicarboxylic acid anhydride was used in step f instead of indole-5,6-dicarboxylic acid anhydride. The naphthalene substrate was made in several steps from naphthalene-2,3-dicarboxylic acid. ¹H NMR (d⁶-acetone) δ 10.2 (1H, s), 9.0 (2H, s), 8.6-8.1 (3H, m), 7.6-7.1 (9H, m), 5.0 (1H, m), 3.2 (4H, m), 2.4 (6H, m), 1.8 (3H, s), 1.6 (12H, m).

20

25 The compound was further characterised and tested as the di-N-methyl-D-glucamine salt found: C, 53.14; H, 6.75; N, 5.61. C₅₈H₇₇N₅O₂₁ .6.9 H₂O requires C, 53.40 H, 7.02; N, 5.40%

30 Example 55 3-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-2-(1-adamantanemethylaminocarbonyl)-5-nitronaphthalene and its regioisomer with groups at positions 2 and 3 reversed.

35 This was prepared essentially as in example 24 except that 5-nitronaphthalene-2,3-dicarboxylic acid anhydride was used in step f instead of indole-5,6-dicarboxylic acid anhydride and no attempt was made to separate the regioisomers in step

- h. The naphthalene substrate was made in several steps from naphthalene-2,3-dicarboxylic acid. The deprotection of the dibenzyl ester without reduction of the nitro group was performed using phase transfer hydrogenation over 10% palladium on charcoal using formic acid as a source of hydrogen. ¹H NMR (d⁶-DMSO) δ 10.2 (1H, 2 x s), 9.0 and 8.8 (1H, 2 x d), 8.6-8.0 (4H, m), 7.6-7.1 (10H, m), 4.7 (1H, m), 3.2 (4H, m), 1.8 (3H, s), 1.5 (12H, m).
- 10 The compound was further characterised and tested as the di-N-methyl-D-glucamine salt found: C, 51.97; H, 6.70; N, 6.12. C₅₄H₇₂N₆O₁₉ . 3.5 H₂O. 3.5 HCOOH requires C, 51.80; H, 6.50; N, 6.30%
- 15 Example 56 3-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-2-(1-adamantanemethylaminocarbonyl)-1-phenylnaphthalene and its regioisomer with groups at positions 2 and 3 reversed.
- 20 This was prepared essentially as in example 24 except that 1-phenylnaphthalene-2,3-dicarboxylic acid anhydride was used in step f instead of indole-5,6-dicarboxylic acid anhydride and no attempt was made to separate the regioisomers in step h. The naphthalene substrate was made from 2-phenylpropionic acid as described in J.Het.Chem., 1974, 11(5), 687-90. ¹H NMR (d⁶-DMSO) δ 10.1 (1H, s), 9.8 (1H, d), 9.4 (2H, s), 8.2 (1H, s), 8.0-7.0 (16H, m), 4.8 (1H, m), 3.1 (2H, m), 2.4 (2H, m), 1.6 (3H, s), 1.4 (6H, m), 0.9 (6H, s).
- 25 acid as described in J.Het.Chem., 1974, 11(5), 687-90. ¹H NMR (d⁶-DMSO) δ 10.1 (1H, s), 9.8 (1H, d), 9.4 (2H, s), 8.2 (1H, s), 8.0-7.0 (16H, m), 4.8 (1H, m), 3.1 (2H, m), 2.4 (2H, m), 1.6 (3H, s), 1.4 (6H, m), 0.9 (6H, s).
- 30 The compound was further characterised and tested as the N-methyl-D-glucamine salt found: C, 65.46; H, 6.89; N, 5.41. C₅₃H₆₀N₄O₁₂ . 1.7 H₂O requires C, 65.23; H, 6.55; N, 5.74%
- Example 57 3-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-2-(1-adamantanemethylaminocarbonyl)-1,2,3,4-tetrahydroisoquinoline
- 35 a. -N-tert-butyloxycarbonyl-3-(1S-(3,5-dibenzoyloxycarbonyl-

phenylaminocarbonyl)-2-phenylethylaminocarbonyl)-1,2,3,4-tetrahydroisoquinoline

(±)-N-tert-butyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-
5 3- carboxylic acid (831 mg, 3 mmol) was suspended in dichloromethane (30 ml) and diisopropylethylamine (1.56 ml, 9 mmol) and PyBOP (500 mg, 3 mmol) was added. After stirring for 5 min, 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-
2-phenylethylamine (prepared as indicated in example 15)
10 (1.52 g, 3 mmol) was added. After stirring the mixture for 2h the organic solution was washed with 5% potassium hydrogensulphate solution (30 ml) and brine (30 ml) and dried over magnesium sulphate. The organic solution was filtered and evaporated to leave a gum that was purified by
15 column chromatography (silica dichloromethane 85% and ethyl acetate 15%) to leave the title compound (1.87 g).

b. 3-(1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-1,2,3,4-tetrahydroisoquinoline
20

The product of step a (1.87 g) was treated with trifluoroacetic acid (20 ml) for 20 min. After evaporation the material was partitioned between 5% sodium hydrogencarbonate solution and ethyl acetate. The insoluble
25 white solid formed was filtered off and dried in vacuo (0.92g).

c. 3-(1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-2-(1-adamantanemethylamino-
30 carbonyl)-1,2,3,4-tetrahydroisoquinoline

The product of step b (1.75 g, 2.6 mmol) was dissolved in dichloromethane (40 ml) and 1-adamantanemethylisocyanate (0.6 g, 3.1 mmol) was added. The solution was stirred at
35 room temperature overnight. The solution was then washed with 2M hydrochloric acid and brine, dried and evaporated to leave a solid that was purified by recrystallisation from ethanol followed by column chromatography (silica

dichloromethane 80% and ethyl acetate 20%) to leave the title compound.

d. 3-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethyl-aminocarbonyl)-2-(1-adamantanemethylaminocarbonyl)-1,2,3,4-tetrahydroisoquinoline

This was prepared essentially as described in example 3 step b except that the product of step c was used as substrate instead of 3-(2R-benzyloxycarbonyl-pyrrolidino-carbonyl)-2-(1-adamantanemethylaminocarbonyl)-naphthalene. ¹H NMR (d⁶-DMSO) δ 10.1 (1H, 2 x s), 8.5 (2H, 2 x s), 8.3 and 7.8 (1H, 2x d), 8.2 (1H, s), 7.3-6.8 (9H, m), 6.5 and 6.4 (1H, 2 x t), 4.7-4.2 (4H, m), 3.2-2.7 (6H, m), 1.8 (3H, m), 1.5 (6H, m), 1.3 (6H, m).

The compound was further characterised and tested as the di-N-methyl-D-glucamine salt found: C, 57.23; H, 7.42; N, 7.61. C₅₃H₇₆N₆O₁₇ .2.5 H₂O requires C, 57.13; H, 7.33; N, 7.54%

Example 58 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-ethylaminocarbonyl)-6-(cycloheptanemethylaminocarbonyl)-indole and regioisomer with substituents at positions 5 and 6 reversed

The material was prepared essentially as in example 42 except that 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-ethylamine was used in step h instead of 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine and that no attempt was made to separate the regioisomers at the end of this stage. The 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-ethylamine was prepared essentially as in example 15 steps c and d except that BOC-L-alanine was used in step c instead of BOC-L-phenylalanine. ¹H NMR (d⁶-DMSO) δ 11.5 (1H, s), 10.2 (1H, s), 8.7 (4H, m), 8.2 (1H, s), 7.6 (3H, m), 6.5 (1H, s), 4.5 (1H, m), 3.1 (2H, m), 1.6-1.0 (16H, m).

The compound was further characterised and tested as the di-
N-methyl-D-glucamine salt found: C, 54.88; H, 7.16; N, 8.98.
 $C_{43}H_{66}N_6O_{17}$, requires C, 55.00; H, 7.09; N, 8.95%

5 Example 59 5-(1R-(3,5-dicarboxyphenylaminocarbonyl)-
ethylaminocarbonyl)-6-(cycloheptanemethylaminocarbonyl)-
indole and regioisomer with substituents at positions 5 and
6 reversed

10 The material was prepared essentially as in example 58
except that 1R-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-
ethylamine was used in step h instead of 1S-(3,5-
dibenzyloxycarbonylphenylaminocarbonyl)-ethylamine. The 1R-
(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-ethylamine was
15 prepared essentially as in example 15 steps c and d except
that BOC-D-alanine was used in step c instead of BOC-L-
phenylalanine. 1H NMR (d_6 -DMSO) δ 11.5 (1H, s), 10.2 (1H, s),
8.7 (4H, m), 8.2 (1H, s), 7.6 (3H, m), 6.5 (1H, s), 4.5 (1H,
m), 3.1 (2H, m), 1.6-1.0 (16H, m).

20

The compound was further characterised and tested as the di-
N-methyl-D-glucamine salt found: C, 52.76; H, 7.24; N, 8.60.
 $C_{43}H_{66}N_6O_{17} \cdot 2H_2O$ requires C, 52.96; H, 7.24; N, 8.62%

25 Example 60 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-(4-
hydroxyphenyl)ethylaminocarbonyl)-6-(1-adamantanemethyl-
aminocarbonyl)-benzimidazole

This was prepared essentially as in example 25 except that
30 1S-(3,5-dibenzyloxycarbonyl-phenylaminocarbonyl)-2-(4-
hydroxyphenyl)ethylamine was used in step d instead of 1S-
(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethyl-
amine. The 1S-(3,5-dibenzyloxy-carbonylphenylaminocarbonyl)-
2-(4-hydroxyphenyl)ethylamine was prepared as outlined in
35 example 30. 1H NMR (d_6 -DMSO) δ 13.0 (3H, br s), 10.2 (1H, s),
9.3 (1H, br s), 8.8 (1H, d), 8.7 (2H, s), 8.5 (1H, t), 8.4
(1H, s), 8.2 (1H, s), 7.9 (1H, s), 7.2 (1H, s), 7.1 (2H, d),
6.7 (2H, d), 4.6 (1H, m), 3.0-2.3 (4H, m), 1.8 (3H, s), 1.6

(6H, m), 1.4 (6H, m).

The compound was further characterised and tested as the di-
N-methyl-D-glucamine salt found: C, 56.79; H, 6.75; N, 8.98.

5 C₅₁H₇₁N₇O₁₆ requires C, 57.24; H, 6.69; N, 9.16%

Example 61 5-(1R-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

10

This was prepared essentially as in example 25 except that 1R-(3,5-dibenzyloxycarbonyl-phenylaminocarbonyl)-2-phenylethylamine was used in step d instead of 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine.

15 The 1R-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine was prepared as outlined in example 29. ¹H NMR (d⁶-DMSO) δ 13.0 (3H, br s), 10.2 (1H, s), 8.9 (1H, d), 8.7 (2H, s), 8.5 (1H, t), 8.4 (1H, s), 8.2 (1H, s), 7.9 (1H, s), 7.4 (5H, m), 7.1 (1H, s), 4.7 (1H, m), 3.5-2.6 (4H, m),
20 1.8 (3H, s), 1.4 (12H, m).

The compound was further characterised and tested as the di-
N-methyl-D-glucamine salt found: C, 54.96; H, 7.33; N, 8.83.
C₅₁H₇₁N₇O₁₇ .3.5H₂O requires C, 54.79; H, 7.04; N, 8.77%

25

Example 62 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-cycloheptanemethylaminocarbonyl)-benzimidazole

30 The material was prepared essentially as in example 25 except that cycloheptanemethylamine was used in step c instead of 1-adamantanemethylamine, ¹H NMR (d⁶-DMSO) δ 13.2 (2H, br s), 12.8 (1H, br s), 10.2 (1H, s), 8.9 (1H, d), 8.7 (2H, s), 8.6 (1H, t), 8.4 (1H, s), 8.2 (1H, s), 8.0 (1H, m),
35 7.4 (5H, m), 7.1 (1H, s), 4.7 (1H, m), 3.5-2.9 (4H, m), 1.7-1.4 (13H, m).

The compound was further characterised and tested as the di-

N-methyl-D-glucamine salt found: C, 56.48; H, 6.73; N, 9.40.
C₄₈H₆₉N₇O₁₇ requires C, 56.74; H, 6.84; N, 9.65%

Example 63 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-(2-fluorophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

This was prepared essentially as in example 25 except that 1S-(3,5-dibenzoyloxycarbonyl-phenylaminocarbonyl)-2-(2-fluorophenyl)ethylamine was used in step d instead of 1S-(3,5-dibenzoyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine. The 1S-(3,5-dibenzoyloxycarbonylphenylaminocarbonyl)-2-(2-fluorophenyl)ethylamine was prepared as outlined in example 27. ¹H NMR (d⁶-DMSO) δ 13.0 (3H, br s), 10.2 (1H, s), 8.9 (1H, d), 8.7 (2H, s), 8.6 (1H, t), 8.4 (1H, s), 8.2 (1H, s), 7.9 (1H, d), 7.4-7.2 (4H, m), 7.1 (1H, s), 4.8 (1H, m), 3.6-2.9 (4H, m), 1.8 (3H, s), 1.6 (6H, m), 1.3 (6H, m).

The compound was further characterised and tested as the di-N-methyl-D-glucamine salt found: C, 55.19; H, 6.77; N, 8.66.
C₅₁H₇₆FN₇O₁₈ requires C, 55.10; H, 6.75; N, 8.82%

Example 64 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-(4-aminophenyl)-ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

This was prepared as outlined in example 31 except that benzimidazole-5,6-dicarboxylic acid anhydride was used as substrate in step g instead of indole-5,6-dicarboxylic acid anhydride and there was no need to separate any regioisomers as these could not arise in this reaction. ¹H NMR (d⁶-DMSO) δ 12.8 (1H, br s), 10.2 (1H, s), 8.8 (1H, d), 8.7 (2H, s), 8.5 (1H, t), 8.4 (1H, s), 8.2 (1H, s), 7.9 (1H, br s), 7.3 (1H, s), 7.0 (2H, d), 6.6 (2H, d), 4.6 (1H, m), 3.3-2.8 (4H, m), 1.9 (3H, s), 1.6 (6H, m), 1.2 (6H, m).

The compound was further characterised and tested as the N-methyl-D-glucamine salt found: C, 56.83; H, 6.49; N, 10.79.

$C_{44}H_{55}N_7O_{12} \cdot 3.0 H_2O$ requires C, 57.04; H, 6.62; N, 11.22%

Example 65 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-5-aminopentylaminocarbonyl)-6-(1-adamantanemethylamino-carbonyl)-indole and regioisomer with substituents at positions 5 and 6 reversed

This was prepared essentially as in example 24 except that 1S-(3,5-dibenzyloxycarbonyl-phenylaminocarbonyl)-5-benzyloxycarbonylaminopentylamine was used in step h instead of 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine and the mixture of regioisomers formed during this step were not separated. The 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-5-benzyloxycarbonylaminopentylamine was prepared essentially as in example 15 steps c and d except that α -BOC- ϵ -Z-lysine was used in step c instead of BOC-L-phenylalanine. 1H NMR (d_6 -DMSO) δ 11.5 (1H, 2 x s), 10.2 (1H, 2 x s), 8.8-8.2 (4H, m), 7.9-7.2 (4H, m), 6.5 (1H, 2 x s), 5.3 (1H, s), 5.0 (1H, s), 4.5 (1H, m), 3.2 (4H, m), 2.0-1.0 (21H, m).

The compound was further characterised and tested as the N-methyl-D-glucamine salt found: C, 60.36; H, 7.02; N, 9.98. $C_{42}H_{56}N_6O_{12}$ requires C, 60.13; H, 6.97; N, 10.02%

25

Example 66 5-(1S-(3,5-diethoxycarbonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole and regioisomer with substituents at positions 5 and 6 reversed

30

This was prepared essentially as in example 24 except that 1S-(3,5-ethoxycarbonyl-phenylaminocarbonyl)-2-phenylethylamine was used in step h instead of 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine and the mixture of regioisomers formed during this step were not separated. No hydrogenation was required. 1S-(3,5-ethoxycarbonyl-phenylaminocarbonyl)-2-phenylethylamine was prepared as outlined in example 15 steps c and d except that

3,5-diethoxycarbonylaniline was used in step c instead of 3,5-dibenzyloxycarbonylaniline. found: C, 69.88; H, 6.59; N, 7.67. $C_{42}H_{46}N_4O_6$ requires C, 70.18; H, 6.45; N, 7.79% 1H NMR (d^6 -DMSO) δ 11.5 (1H, s), 10.3 and 10.2 (1H, 2 x s), 8.8 (3H, m), 8.5 (1H, t), 8.2 (1H, s), 7.9 and 7.7 (1H, 2 x s), 7.5-7.2 (6H, m), 7.0 (1H, 2 x s), 6.5 (1H, 2 x s), 4.7 (1H, m), 4.4 (4H, q), 3.4 and 2.9 (4H, m), 1.8 (3H, s), 1.5 (6H, m), 1.4 (6H, s), 1.3 (6H, t).

10 Example 67 5-(1S-(4-fluorophenylmethylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

This was prepared essentially as in example 25 except that 15 1S-(4-fluorophenylmethylaminocarbonyl)-2-phenylethylamine was used in step d instead of 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine and no final deprotection step was required. The 1S-(4-fluorophenylmethylaminocarbonyl)-2-phenylethylamine was prepared by 20 coupling BOC-L-phenylalanine NHS ester with 4-fluorobenzylamine in DME followed by treatment with trifluoroacetic acid. Found: C, 71.14; H, 6.43; N, 11.39. $C_{36}H_{38}FN_5O_3$ requires C, 71.15; H, 6.30; N, 11.52% 1H NMR (d^6 -DMSO) δ 11.3 (1H, br s), 8.7 (2H, m), 8.5 (2H, br s), 7.8 (1H, s), 7.4-7.1 (10H, m), 4.6 (1H, m), 4.4 (2H, m), 3.4 (2H, m), 2.8 (2H, m), 1.9 (3H, s), 1.6 (6H, m), 1.4 (6H, s).

25 Example 68 5-(1S-(4-fluorophenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-30 benzimidazole

This was prepared essentially as in example 25 except that 1S-(4-fluorophenylaminocarbonyl)-2-phenylethylamine was used in step d instead of 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine and no final deprotection 35 step was needed. The 1S-(4-fluorophenylaminocarbonyl)-2-phenylethylamine was prepared by coupling BOC-L-phenylalanine with 4-fluoroaniline using PyBrOP, followed by

treatment with trifluoroacetic acid. Found: C, 70.62; H, 6.26; N, 11.75. $C_{35}H_{36}FN_5O_3$ requires C, 70.81; H, 6.11; N, 11.80% 1H NMR (d^6 -DMSO) δ 12.8 (1H, br s), 10.0 (1H, br s), 8.8 (1H, m), 8.6 (1H, br s), 8.4 (1H, s), 7.9 (3H, m), 7.8-7.1 (8H, m), 4.7 (1H, m), 3.5 (1H, m), 3.1 (1H, m), 2.9 (2H, m), 1.9 (3H, s), 1.6 (12H, m).

Example 69 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-(2,4-imidazolyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

This was prepared essentially as in example 25 except that 1S-(3,5-dibenzoyloxycarbonylphenylaminocarbonyl)-2-(2,4-imidazolyl)ethylamine was used in step d instead of 1S-(3,5-dibenzoyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine. The 1S-(3,5-dibenzoyloxycarbonylphenylaminocarbonyl)-2-(2,4-imidazolyl)ethylamine was prepared by coupling BOC-L-histidine (with the aromatic ring nitrogen protected with a BOM group) to 3,5-dibenzoyloxycarbonylaniline using PyBrOP, followed by treatment with trifluoroacetic acid. 1H NMR (d^6 -DMSO) δ 10.1 (1H, br s), 8.8 (1H, m), 8.6 (2H, br s), 8.5 (1H, br s), 8.4 (1H, s), 8.2 (1H, s), 7.9 (1H, s), 7.6 (1H, s), 7.5 (1H, s), 6.9 (1H, s), 4.7 (1H, m), 3.2-3.0 (4H, m), 1.8 (3H, s), 1.5 (12H, m).

Example 70 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-(2-fluorophenyl)ethylaminocarbonyl)-6-(cycloheptanemethylaminocarbonyl)-benzimidazole

This was prepared essentially as in example 63 except that cycloheptanemethylamine was used instead of 1-adamantanemethylamine in step c, 1H NMR (d^6 -DMSO) δ 13.0 (3H, br s), 10.2 (1H, br s), 8.9 (1H, d), 8.74 (2H, s), 8.7 (1H, t), 8.4 (1H, s), 8.2 (1H, s), 7.8 (1H, s), 7.5-7.1 (5H, m), 4.8 (1H, m), 3.5 (1H, m), 3.3-3.1 (3H, m), 1.6-1.1 (13H, m).

The compound was further characterised and tested as the di-N-methyl-D-glucamine salt. Found: C, 55.39; H, 6.85; N,

9.17. $C_{48}H_{68}FN_7O_{17}$ requires C, 55.75; H, 6.63; N, 9.48%

Example 71 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-
ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-
5 benzimidazole

This was prepared essentially as in example 25 except that
1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-ethylamine
was used in step d instead of 1S-(3,5-dibenzyloxycarbonyl-
10 phenylaminocarbonyl)-2-phenylethylamine. The 1S-(3,5-
dibenzyloxycarbonylphenylaminocarbonyl)-ethylamine was
prepared by coupling BOC-L-alanine to 3,5-dibenzyloxy-
carbonylaniline using PyBrOP, followed by treatment with
trifluoroacetic acid. 1H NMR (d^6 -DMSO) δ 13.0 (3H, br s),
15 10.1 (1H, br s), 8.8 (1H, d), 8.7 (2H, s), 8.5 (1H, t), 8.4
(1H, s), 8.2 (1H, s), 7.9 (1H, s), 7.7 (1H, s), 4.5 (1H, m),
3.0 (2H, m), 1.8 (3H, s), 1.6-1.4 (15H, m).

The compound was further characterised and tested as the di-
20 N-methyl-D-glucamine salt. Found: C, 50.76; H, 7.23; N,
8.97. $C_{45}H_{67}N_7O_{17}$ requires C, 50.60; H, 7.27; N, 9.18%

Example 72 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-
ethylaminocarbonyl)-6-(cycloheptanemethylaminocarbonyl)-
25 benzimidazole

This was prepared essentially as in example 71 except that
cycloheptanemethylamine was used instead of 1-adamantane-
methylamine in step c, 1H NMR (d^6 -DMSO) δ 13.0 (3H, br s),
30 10.2 (1H, br s), 8.8 (1H, d), 8.7 (2H, s), 8.6 (1H, t), 8.4
(1H, s), 8.2 (1H, s), 7.9 (1H, s), 7.7 (1H, br s), 4.5 (1H,
m), 3.1 (2H, m), 1.8-1.1 (16H, m).

The compound was further characterised and tested as the di-
35 N-methyl-D-glucamine salt. Found: C, 51.34; H, 7.29; N,
9.89. $C_{42}H_{65}FN_7O_{17} \cdot 2.5 H_2O$ requires C, 51.25; H, 7.16; N,
9.96%

Example 73 5-(1S-(3,5-dicarboxyphenyl-N-(methyl)amino-carbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantane-methylaminocarbonyl)-benzimidazole

5 This was prepared essentially as in example 25 except that 1S-(3,5-dibenzyloxycarbonylphenyl-N-(methyl)-aminocarbonyl)-2-phenylethylamine was used in step d instead of 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine. The 1S-(3,5-dibenzyloxycarbonylphenyl-N-(methyl)-amino-
10 carbonyl)-2-phenylethylamine was prepared by treatment of N-t-butyloxycarbonyl-1S-(3,5-dibenzyloxycarbonylphenyl-aminocarbonyl)-2-phenylethylamine sodium hydride and methyl iodide, followed by treatment with trifluoroacetic acid. ¹H
NMR (d⁶-DMSO) δ 13.0 (3H, br s), 8.8 (1H, d), 8.4 (2H, s),
15 8.0 (3H, m), 7.7 (2H, m), 7.2 (3H, m), 6.9 (2H, s), 4.5 (1H, m), 3.3-2.8 (7H, m), 1.9 (3H, s), 1.6-1.4 (12H, m).

The compound was further characterised and tested as the di-N-methyl-D-glucamine salt. Found: C, 56.43; H, 7.25; N,
20 8.82. C₅₂H₇₃N₇O₁₇ requires C, 56.27; H, 7.05; N, 8.83%

Example 74 N-methyl-5-(1S-(3,5-dicarboxyphenylamino-carbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole, mixture of regioisomers

25

This was prepared essentially as in example 25 except that N-methyl-benzimidazole-5,6-dicarboxylic acid anhydride was used in step c instead of benzimidazole-5,6-dicarboxylic acid anhydride. This was prepared by treatment of
30 dimethylbenzimidazole-5,6-dicarboxylate with sodium methoxide and methyl iodide, followed by saponification with potassium hydroxide, and anhydride formation with acetic anhydride. ¹H NMR (d⁶-DMSO) δ 13.0 (2H, br s), 10.2 (1H, s), 8.8 (1H, m), 8.7 (2H, s), 8.6 (2H, m), 8.2 (1H, s), 8.0 and
35 7.9 (1H, 2 x s), 7.4-7.0 (6H, m), 4.8 (1H, m), 3.9 (3H, 2 x s), 3.6-2.5 (4H, m), 1.8 (3H, s), 1.6-1.4 (12H, m).

The compound was further characterised and tested as the di-

N-methyl-D-glucamine salt. Found: C, 55.64; H, 7.15; N, 8.81. $C_{52}H_{73}N_7O_{17} \cdot 3H_2O$ requires C, 55.65; H, 7.10; N, 8.74%

Example 75 5-(1S-(3-carboxy-4-fluoro-phenylaminocarbonyl))-
5 2-phenylethylaminocarbonyl)-6-(1-adamantanemethyl-aminocarbonyl)-benzimidazole

This was prepared essentially as in example 25 except that
1S-(3-benzyloxycarbonyl-4-fluoro-phenylaminocarbonyl)-2-
10 phenylethylamine was used in step d instead of 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine.
The 1S-(3-benzyloxycarbonyl-4-fluoro-phenylaminocarbonyl)-2-phenylethylamine was prepared by coupling BOC-L-phenylalanine with 3-benzyloxycarbonyl-4-fluoroaniline using
15 PyBrOP, followed by treatment with trifluoroacetic acid. 1H NMR (d^6 -DMSO) δ 13.2 (1H, br s), 12.8 (1H, br s), 10.1 (1H, s), 8.8 (1H, d), 8.6 (1H, t), 8.4 (2H, m), 8.1 (1H, m), 8.0 (1H, m), 7.4 (4H, s), 7.3 (2H, m), 7.1 (1H, br s), 4.5 (1H, m), 3.3-2.8 (4H, m), 1.9 (3H, s), 1.6-1.4 (12H, m).

20

The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 59.00; H, 7.08; N, 8.55. $C_{43}H_{53}N_6O_{10} \cdot 2.9 H_2O \cdot 1.3$ dioxan requires C, 56.27; H, 7.05; N, 8.83%

25

Example 76 5-(2R-carboxymethylaminocarbonylpyrrolidinocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

This was prepared essentially as in example 25 except that
30 2R-benzyloxycarbonylmethylaminocarbonylpyrrolidine was used in step d instead of 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine. 1H NMR (d^6 -DMSO) δ 12.8 (1H, br s), 12.5 (1H, br s), 8.7-7.5 (5H, m), 4.5 (1H, m), 3.9 (1H, dd), 3.6 (2H, m), 3.3 (2H, m), 2.9 (1H, m), 2.1-1.5
35 (19H, m).

The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 56.93; H, 7.42; N, 10.76.

$C_{34}H_{50}N_6O_{10} \cdot 1.4H_2O$ requires C, 57.25; H, 7.48; N, 10.43%

Example 77 5-(2S-(3,5-dicarboxyphenylaminocarbonyl)-pyrrolidinocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-5 benzimidazole

This was prepared essentially as in example 25 except that 2S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-pyrrolidine was used in step d instead of 1S-(3,5-dibenzyloxycarbonyl-phenylaminocarbonyl)-2-phenylethyl amine. The 2S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-pyrrolidine was prepared by coupling BOC-L-proline with 3,5-dibenzyloxycarbonylaniline using PyBrOP, followed by treatment with trifluoroacetic acid. 1H NMR (d_6 -DMSO) δ 13.0 (3H, br s), 10.1 (1H, s), 8.7 (3H, m), 8.4 (1H, s), 8.2 (1H, s), 7.6 (1H, br s), 4.6 (1H, m), 3.7-3.1 (2H, m), 3.0 (2H, d), 2.3 and 2.1 (2H, m), 1.8 (3H, s), 1.7-1.4 (12H, m).

The compound was further characterised and tested as the di-N-methyl-D-glucamine salt. Found: C, 56.93; H, 7.42; N, 10.76. $C_{47}H_{69}N_7O_{17} \cdot 1.4 H_2O$ requires C, 57.25; H, 7.48; N, 10.43%

Example 78 5-(1S-(2,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

This was prepared essentially as in example 25 except that 1S-(2,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethyl amine was used in step d instead of 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethyl amine. The 1S-(2,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethyl amine was prepared by coupling FMOC-L-phenylalanine acid chloride with 2,5-dibenzyloxycarbonylaniline, followed by treatment with piperidine. 1H NMR (d_6 -DMSO) δ 13.2 (2H, br s), 11.7 (1H, br s), 9.1 (1H, d), 9.0 (1H, s), 8.4 (1H, s), 8.0 (2H, m), 7.7 (3H, m), 7.4 (3H, m),

7.3 (2H, m), 7.2 (1H, m), 4.7 (1H, m), 3.4 (1H, dd), 3.1 (1H, dd), 2.8 (2H, m), 1.8 (3H, s), 1.6 (6H, q), 1.4 (6H, m).

- 5 The compound was further characterised and tested as the di-N-methyl-D-glucamine salt. Found: C, 59.00; H, 7.08; N, 8.55. $C_{43}H_{53}N_6O_{10} \cdot 2.9 H_2O$. 1.3 dioxan requires C, 59.03; H, 7.11; N, 8.57%

- 10 Example 79 5-(1S-(3-carboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

- a. 5-(1S-(3-benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-benzimidazole-6-carboxylic acid

The product of example 25 step b (1.23g, 6.5 mmol) and 1S-(3-benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine (3.97 g, 6.5 mmol) were dissolved in acetonitrile (50 ml) and stirred and heated at reflux for 1h. After cooling a yellow crystalline solid was formed which was isolated by filtration, washed with acetonitrile and dried to yield the title compound (3.65 g). The 1S-(3-benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine had been prepared by coupling BOC-L-phenylalanine and 3-benzyloxycarbonylaniline in the presence of PyBROP followed by treatment with trifluoroacetic acid.

- b. 5-(1S-(3-benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

The product of step a (1.12 g, 2 mmol), 4-hydroxybenzotriazole (270 mg, 2 mmol), EDC (409 mg, 2 mmol), 1-adamantanemethylamine (495 mg, 3 mmol) and DMAP (20 mg) were dissolved in dry DMF (4 ml). After stirring overnight at room temperature the mixture was poured onto water (30 ml) and the resulting white precipitate was filtered and dried

in vacuo to yield the title compound (1.51 g).

c. 5-(1S-(3-carboxyphenylaminocarbonyl)-2-phenylethylamino-carbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

5

This was prepared essentially as in example 24 step i except that the benzyl ester prepared in step b above was used as substrate instead of the product of example 24 step h. ¹H NMR (d⁶-DMSO) δ 13.2 (2H, br s), 10.1 (1H, d), 8.9 (1H, d), 8.6 (2H, m), 8.4 (1H, s), 8.1 (1H, m), 7.9 (1H, s), 7.7 (1H, m), 7.4 (6H, m), 7.1 (1H, s), 4.8 (1H, m), 3.2-2.9 (4H, m), 1.9 (3H, s), 1.6 (6H, q), 1.4 (6H, m).

The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 60.70; H, 6.92; N, 9.89. C₄₃H₅₄N₆O₁₀ .2.0 H₂O requires C, 60.69; H, 6.87; N, 9.88%

Example 80 5-(1S-(3,5-ditetrazolylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

a. Bis pivaloyloxymethyl derivative of 1S-(3,5-ditetrazolylphenylaminocarbonyl)-2-phenylethylamine

25 5-nitro isophthalic acid was converted to 5-nitro-3-cyanobenzonitrile via the bis primary amide. Treatment with sodium azide in hot DMF gave the bis tetrazole which was derivatised with POM chloride. Catalytic hydrogenation of the nitro group gave the aniline, which was coupled with BOC-L-phenylalanine using PyBROP and treated with trifluoroacetic acid to leave the title compound.

b. Bis pivaloyloxymethyl derivative of 5-(1S-(3,5-ditetrazolylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

This was prepared essentially as in example 79 steps a and b but using the product of this example step a as substrate

in step a instead of 1S-(3-benzyloxycarbonylphenylamino-carbonyl)-2-phenylethylamine

c. 5-(1S-(3,5-ditetrazolylphenylaminocarbonyl)-2-phenyl-ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

The bis POM derivative prepared in step b (890 mg) was dissolved in saturated methanolic ammonia solution (20 ml) and stirred at room temperature for 5h. The volatile material was removed by evaporation to leave the title compound (740 mg) as its bis ammonium salt, Found: C, 57.36; H, 6.06; N, 27.17. $C_{37}H_{43}N_{15}O_3 \cdot 1.5 H_2O$ requires C, 57.50; H, 5.99; N, 27.18% , 1H NMR (d^6 -DMSO) δ 10.2 (1H, s), 8.8 (1H, d), 8.6 (2H, d), 8.4 (2H, m), 7.9 (1H, s), 7.4 -7.2 (7H, m), 4.8 (1H, m), 3.5-3.0 (4H, m), 1.8 (3H, s), 1.5 (6H, q), 1.4 (6H, s).

Example 81 5-(1S-(3,5-dimethoxycarbonylphenylamino-carbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

This was prepared essentially as in example 79 except that 1S-(3,5-dimethoxycarbonylphenylaminocarbonyl)-2-phenylethylamine was used in step a instead of 1S-(3-benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine, 1H NMR (d^6 -DMSO) δ 12.8 (1H, 2 x s), 10.3 and 10.2 (1H, 2 x s), 8.9 (1H, t), 8.8 (2H, s), 8.6 (1H, m), 8.4 (1H, s), 8.2 (1H, s), 8.0 and 7.8 (1H, 2 x s), 7.3 (5H, m), 7.2 and 7.1 (1H, 2 x s), 4.8 (1H, m), 3.9 (6H, s), 3.4 (1H, m), 3.0 (3H, m), 1.8 (3H, s), 1.6-1.4 (12H, m).

Example 82 5-(1S-(2-methyl-5-carboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

This was prepared essentially as in example 79 except that 1S-(2-methyl-5-benzyloxycarbonylphenylaminocarbonyl)-2-

phenyl ethylamine was used in step a instead of 1S-(3-benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine, ¹H NMR (d⁶-DMSO) δ 12.8 (2H, s), 9.7 (1H, m), 8.9 (1H, m), 8.5 (1H, s), 8.4 (1H, s), 8.0 (1H, m) 7.7 (2H, m) 7.3 (7H, m), 5 4.7 (1H, m), 3.4-2.7 (4H, m), 2.3 (3H, s), 1.8 (3H, s), 1.6-1.4 (12H, m).

The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 56.87; H, 6.89; N, 9.08.
10 C₄₄H₅₆N₆O₁₀ .5.2 H₂O requires C, 57.23; H, 7.26; N, 9.10%

Example 83 5-(1S-(3-tetrazolylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

15

This was prepared essentially as in example 79 except that the POM derivative of 1S-(3-tetrazolylphenylaminocarbonyl)-2-phenylethylamine was used in step a instead of 1S-(3-benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine.

20 The POM derivative of 1S-(3-tetrazolylphenylaminocarbonyl)-2-phenylethylamine was prepared essentially as in example 80 step a except that the synthetic manipulations were carried out using the commercially available 3-nitrobenzonitrile as starting material. The compound was isolated and tested as
25 its ammonium salt. Found: C, 62.48; H, 6.42; N, 19.72. C₃₆H₄₀N₁₀O₃ .1.8 H₂O requires C, 62.38; H, 6.34; N, 20.20%, ¹H NMR (d⁶-DMSO) δ 10.0 (1H, s), 8.8 (1H, d), 8.6 (1H, s), 8.5 (1H, t), 8.4 (1H, s), 7.9 (1H, s), 7.8 (1H, m), 7.7 (1H, d), 7.4-7.2 (7H, m), 4.8 (1H, m), 3.5-2.9 (4H, m), 1.9 (3H, s),
30 1.5 (6H, q), 1.4 (6H, s).

Example 84 5-(1S-(3,5-ditetrazolylphenylaminocarbonyl)-2-(2-fluorophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

35

This was prepared essentially as in example 80 except that BOC-L-2-fluorophenylalanine was used in step a instead of BOC-L-phenylalanine. The compound was isolated and tested as

its bis ammonium salt. Found: C, 54.97; H, 5.92; N, 26.06. $C_{37}H_{42}FN_{15}O_3 \cdot 2.5 H_2O$ requires C, 54.94; H, 5.85; N, 25.97% , 1H NMR (d^6 -DMSO) δ 10.1 (1H, s), 8.8 (1H, d), 8.4 (5H, m), 7.9 (1H, s), 7.5 (1H, t), 7.4 (1H, t), 7.3 (3H, m), 4.8 (1H, m), 3.6-2.9 (4H, m), 1.8 (3H, s), 1.5 (6H, q), 1.4 (6H, s).

Example 85 (\pm)- 5-(1-(3,5-dicarboxyphenylaminocarbonyl)-2-(2,4-difluorophenyl)ethylaminocarbonyl)-6-(1-adamantane-methylaminocarbonyl)-benzimidazole

10

This was prepared essentially as in example 79 except that (\pm)-1-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-(2,4-difluorophenyl)ethylamine was used in step a instead of 1S-(3-benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine.

15 (\pm)-1-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-(2,4-difluorophenyl)ethylamine was prepared by coupling BOC-2,4-difluorophenylalanine with 3,5-dibenzyloxycarbonylaniline using PyBrOP, followed by treatment with trifluoroacetic acid, 1H NMR (d^6 -DMSO) δ 13.2 (3H, br s), 10.2 (1H, s), 8.9 (1H, d), 8.7 (2H, d), 8.6 (1H, t), 8.4 (1H, s), 8.2 (1H, t), 7.5 (1H, m), 7.3 (2H, m), 7.2 (1H, s), 7.1 (1H, m), 4.8 (1H, m), 3.5 (1H, dd), 3.0 (3H, m), 1.9 (3H, s), 1.6 (6H, q), 1.5 (6H, s).

25 The compound was further characterised and tested as the di-N-methyl-D-glucamine salt. Found: C, 52.83; H, 6.76; N, 8.26. $C_{51}H_{69}F_2N_7O_{17} \cdot 4H_2O$ requires C, 52.67; H, 6.68; N, 8.43%

Example 86 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethyl-(N-methylamino)-carbonyl)-6-(1-adamantane-methylaminocarbonyl)-benzimidazole

This was prepared essentially as in example 79 except that 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethyl-N-methylamine was used in step a instead of 1S-(3-benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine. 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethyl-N-methylamine was prepared by coupling BOC-N-methyl-L-

phenylalanine with 3,5-dibenzoyloxycarbonylaniline using PyBrOP, followed by treatment with trifluoroacetic acid.

The compound was further characterised and tested as the di-
5 N-methyl-D-glucamine salt. Found: C, 55.69; H, 7.04; N, 8.65. $C_{52}H_{73}N_7O_{17} \cdot 2H_2O$ requires C, 56.56; H, 7.03; N, 8.88%

Example 87 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-(2-
10 fluorophenyl)ethylaminocarbonyl)-6-(1-adamantanemethyl-
aminocarbonyl)-indole

This was prepared essentially as in example 26 except that
the less polar regioisomer prepared in step h was used as
the substrate in step i instead of the mixture used in
15 example 26. 1H NMR (d^6 -DMSO) δ 13.3 (2H, br s), 11.8 (1H, s),
10.2 (1H, s), 8.74 (1H, d), 8.7 (2H, s), 8.5 (1H, t), 8.2
(1H, s), 7.8 (1H, s), 7.6-7.2 (6H, m), 6.5 (1H, s), 4.8 (1H,
m), 3.6 (1H, m), 3.0 (3H, m), 1.9 (3H, br s), 1.6 (12H, m).

20 The compound was further characterised and tested as the di-
N-methyl-D-glucamine salt found: C, 55.55; H, 6.89; N, 7.61.
 $C_{52}H_{71}FN_6O_{17} \cdot 2.8 H_2O$ requires C, 55.67; H, 6.89; N, 7.49%

Example 88 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-(2-
25 fluorophenyl)ethylaminocarbonyl)-6-(1-adamantanemethyl-
aminocarbonyl)-indole

This was prepared essentially as in example 26 except that
the more polar regioisomer prepared in step h was used as
30 the substrate in step i instead of the mixture used in
example 26. 1H NMR (d^6 -DMSO) δ 13.3 (2H, br s), 11.5 (1H, s),
10.3 (1H, s), 8.8 (1H, d), 8.7 (2H, s), 8.4 (1H, t), 8.2
(1H, s), 7.9 (1H, s), 7.5-7.2 (5H, m), 7.0 (1H, s), 6.6 (1H,
s), 4.8 (1H, m), 3.6 (1H, m), 3.0 (3H, m), 1.8 (3H, br s),
35 1.6 (12H, m).

The compound was further characterised and tested as the di-
N-methyl-D-glucamine salt found: C, 55.27; H, 7.03; N, 7.49.

$C_{52}H_{71}FN_6O_{17}$. 3.3 H_2O requires C, 55.22; H, 6.92; N, 7.43%

Example 89 5-(2R-(1R-carboxyethylaminocarbonyl)pyrrolidino-carbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole Mixture
5 of regioisomers at positions 5 and 6

This was prepared essentially as in example 24 except that 2R-(1R-benzyloxycarbonylethylaminocarbonyl)pyrrolidine was used in step h instead of 1S-(3,5-dibenzyloxycarbonylphenyl-
10 aminocarbonyl)-2-phenylethyl amine. 1H NMR (d^6 -DMSO) δ 11.4 (1H, 2 x s), 9.0-7.0 (6H, m), 6.5 (1H, 2 x s), 4.5 and 4.2 (2H, 2 x m), 3.6 (2H, m), 3.3 (2H, m), 2.9 (1H, m), 2.1-1.5 (20H, m).

15 The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 54.22; H, 7.28; N, 6.48. $C_{36}H_{53}N_5O_{10}$. 1.3 DCM. 2.8 dioxan requires C, 54.29; H, 7.33; N, 6.53%

20 Example 90 5-(1S-(3-carboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole Mixture of regioisomers at positions 5 and 6

This was prepared essentially as in example 79 except that
25 indole-5,6-dicarboxylic acid anhydride was used as substrate instead of benzimidazole-5,6-dicarboxylic acid anhydride in step a. 1H NMR (d^6 -DMSO) δ 11.5 (1H, br s), 10.2 and 10.1 (1H, 2 x s), 8.8 (1H, m), 8.5 (2H, m), 8.1 (1H, m), 7.9 and 7.7 (1H, 2 x s), 7.7-7.4 (8H, m), 7.1 and 7.0 (1H, 2 x s),
30 6.6 and 6.5 (1H, 2 x s), 4.7 (1H, m), 3.5-2.9 (4H, m), 1.9 (3H, s), 1.6 (6H, q), 1.5 (6H, m).

The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 61.67; H, 7.11; N, 7.90.
35 $C_{44}H_{55}N_5O_{10}$. 2.5 H_2O requires C, 61.52; H, 7.04; N, 8.15%

Example 91 5-(1R-(carboxymethylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-

indole Mixture of regioisomers at positions 5 and 6

This was prepared essentially as in example 90 except that the benzyl ester of D-phenylalanyl-glycine was used as substrate instead of 1S-(3-benzyloxycarbonylphenylamino-carbonyl)-2-phenylethylamine in step a. ¹H NMR (d⁶-DMSO) δ 11.4 (1H, 2 x s), 8.6 (1H, m), 8.5 (1H, m), 8.3 (1H, m), 7.8 and 7.6 (1H, 2 x s), 7.5-7.1 (7H, m), 6.6 and 6.5 (1H, 2 x s), 4.6 (1H, m), 3.9-2.9 (6H, m), 1.9 (3H, s), 1.6 (6H, q), 1.5 (6H, m).

The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 52.75; H, 7.77; N, 7.52. C₃₉H₅₅N₅O₁₀ .7.5 H₂O requires C, 52.81; H, 7.73; N, 7.89%

Example 92 5-(1S-(3,5-di-methylsulphonylaminophenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole Mixture of regioisomers at positions 5 and 6

a. 1S-(3,5-di-methylsulphonylaminophenylaminocarbonyl)-2-phenylethylamine

This was prepared by in several steps by coupling BOC-L-phenylalaninemethyl ester with 3,5-dinitroaniline using trimethylaluminium in toluene, followed by catalytic hydrogenation to yield the bis aniline. Treatment with methanesulphonic anhydride and subsequent deprotection with TFA gave the title compound.

b. 5-(1S-(3,5-di-methylsulphonylaminophenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole Mixture of regioisomers at positions 5 and 6

The title compound was prepared essentially as in example 24 step h except that the product of step a above was used as substrate rather than 1S-(3,5-dibenzyloxycarbonyl-

phenylaminocarbonyl)-2-phenylethylamine. ^1H NMR (d^6 -DMSO) δ 11.5 (1H, br s), 10.1 and 10.0 (1H, 2 x s), 8.7 (1H, dd), 8.3 (1H, m), 8.1-6.5 (14H, m), 4.8 (1H, m), 3.5 (6H, s), 3.5-3.0 (4H, m), 1.9 (3H, s), 1.6 (6H, q), 1.5 (6H, m).

5

Example 93 5-(1S-(3,5-di-trifluoromethylsulphonylamino-phenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole Mixture of regioisomers at positions 5 and 6

10

This was prepared essentially as in example 92 except that trifluoromethanesulphonic anhydride was used in the course of step a instead of methanesulphonic anhydride Found: C, 51.34; H, 4.48; N, 9.49. $\text{C}_{38}\text{H}_{38}\text{F}_6\text{N}_6\text{O}_7\text{S}_2 \cdot 1.1 \text{H}_2\text{O}$ requires C, 51.41 H, 4.55; N, 9.47% ^1H NMR (d^6 -DMSO) δ 11.5 (1H, br s), 10.1 (1H, 2 x s), 8.7 (1H, m), 8.4 (1H, m), 8.1-6.5 (14H, m), 4.7 (1H, m), 3.5-2.7 (4H, m), 1.9 (3H, s), 1.6 (6H, q), 1.5 (6H, m).

15

20 Example 94 5-(1S-(3,5-di-trifluoromethylcarbonylamino-phenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole Mixture of regioisomers at positions 5 and 6

25 This was prepared essentially as in example 92 except that trifluoroacetic anhydride was used in the course of step a instead of methanesulphonic anhydride Found: C, 54.26; H, 5.66; N, 9.29. $\text{C}_{40}\text{H}_{38}\text{F}_6\text{N}_6\text{O}_5 \cdot 5 \text{H}_2\text{O}$ requires C, 54.13 H, 5.46; N, 9.47% ^1H NMR (d^6 -DMSO) δ 11.5 (1H, br s), 11.4 (2H, br s), 10.2 (1H, 2 x s), 8.7 (1H, m), 8.5 (1H, m), 8.1-6.5 (12H, m), 4.8 (1H, m), 3.5-2.8 (4H, m), 1.8 (3H, s), 1.6 (6H, q), 1.5 (6H, m).

30

Example 95 5-(1S-(3,5-di-tert-butylaminosulphonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole Mixture of regioisomers at positions 5 and 6

35

a. 1S-(3,5-di-tert-butylaminosulphonylphenylaminocarbonyl)-2-phenylethylamine

This was prepared in several steps starting with benzene-5 1,3-disulphonyl chloride. This was nitrated with oleum in nitric acid to give the 5-nitro-1,3-bis sulphonic acid derivative. This was converted to the bis sulphonyl chloride compound with phosphorus pentachloride, and then reacted with tert-butylamine to give the bis tert-butylsulphonamide.

10 Hydrogenation, followed by coupling with Z-L-phenylalanine using PyBROP, gave the title compound as a Z-protected derivative. This was converted to the title compound by hydrogenation.

15 b. 5-(1S-(3,5-di-tert-butylaminosulphonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole Mixture of regioisomers at positions 5 and 6

20 The title compound was prepared essentially as in example 24 step h except that the product of step a above was used as substrate rather than 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine. Found: C, 54.39; H, 6.22; N, 8.07. $C_{44}H_{56}N_6O_7S_2$. 2 DCM. 0.3 ethyl acetate requires C,

25 54.44 H, 6.04; N, 8.07% 1H NMR (d^6 -DMSO) δ 11.4 (2H, m), 8.7 (1H, m), 8.4-6.5 (15H, m), 5.4 (1H, m), 3.1-2.6 (4H, m), 1.9 (3H, s), 1.6 (6H, q), 1.5 (6H, m), 1.1 (18H, m).

Example 96 5-(1S-(3,5-di-aminosulphonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole Mixture of regioisomers at positions 5 and 6

30

The compound of example 95 (30 mg, 0.36 mmol) was treated with trifluoroacetic acid (1ml) and allowed to stir for 24h at room temperature. The solvent was removed by evaporation and the residue was then azeotroped with toluene (3 x 1ml). It was then taken up in dichloromethane (2 ml), and the

35

residual solid that resulted was isolated by filtration, washed with diethyl ether and then dried to yield the title compound (21 mg), ¹H NMR (d⁶-DMSO) δ 11.8 (1H, br s), 11.4 (2H, m), 8.7 (1H, m), 8.4-6.5 (16H, m), 4.8 (1H, m), 3.1-2.6 (4H, m), 1.9 (3H, m), 1.6 (6H, m), 1.5 (6H, m).

Example 97 5-(1S-(3,5-ditetrazolylphenylaminocarbonyl)-2-(2-fluorophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole

10

This was prepared essentially as in example 84 except that indole-5,6-dicarboxylic anhydride was used in in step b instead of benzimidazole-5,6-dicarboxylic anhydride. After the anhydride opening step, the mixture of regioisomers
15 formed was separated by chromatography (silica 5% methanol and 95% dichloromethane) and the more polar regioisomer was taken through the subsequent coupling with 1-adamantane-methylamine and deprotection. ¹H NMR (d⁶-DMSO) δ 11.5 (1H, s), 10.2 (1H, s), 8.7 (1H, d), 8.6 (2H, s), 8.4 (1H, s),
20 8.3(1H, t), 7.7 (1H, s), 7.5-7.0 (6H, m), 6.5 (1H, s), 4.8 (1H, m), 3.6-2.9 (4H, m), 1.8 (3H, s), 1.5 (6H, q), 1.4 (6H, s).

Example 98 6-(1S-(3,5-ditetrazolylphenylaminocarbonyl)-2-(2-fluorophenyl)ethylaminocarbonyl)-5-(1-adamantanemethylaminocarbonyl)-indole

25

This was prepared essentially as in example 97 except that the less polar regioisomer following anhydride opening was
30 used as substrate for subsequent transformations. ¹H NMR (d⁶-DMSO) δ 11.5 (1H, s), 10.3 (1H, s), 8.8 (1H, d), 8.6 (2H, s), 8.4 (1H, s), 8.3(1H, t), 7.9 (1H, s), 7.5-7.0 (6H, m), 6.6 (1H, s), 4.8 (1H, m), 3.6-2.9 (4H, m), 1.8 (3H, s), 1.5 (6H, q), 1.4 (6H, s).

35

Example 99 5-(1S-(3-trifluoroacetylaminosulphonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole Mixture of regioisomers at

positions 5 and 6

a. 1S-(3-trifluoroacetylaminosulphonylphenylaminocarbonyl)-2-phenylethylamine

5

This was prepared in several steps starting with nitrobenzene-3-sulphonyl chloride. This was converted into the sulphonamide using ammonia in benzene. Trifluoroacetic anhydride was used to introduce the trifluoroacetyl group
10 onto the sulphonamide. Catalytic hydrogenation reduced the nitro group to an amino function and this material was coupled to BOC-L-phenylalanine using the PyBROP method. Removal of the BOC group was achieved with trifluoroacetic acid.

15

b. 5-(1S-(3,5-di-tert-butylaminosulphonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole Mixture of regioisomers at
20 positions 5 and 6

20

The title compound was prepared essentially as in example 24 step h except that the product of step a above was used as substrate rather than 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine. ¹H NMR (d⁶-DMSO) δ 11.5
25 (1.5H, m), 10.5-9.8 (1.5 H, m), 8.5-7.0 (14H, m), 6.6 and 6.5 (1H, 2 x s), 4.8 (1H, m), 3.5-2.9 (4H, m), 1.9 (3H, s), 1.7 (6H, m), 1.5 (6H, m).

Example 100 5-(1S-(3-tetrazolylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole
30

This was prepared essentially as in example 83 except that indole-5,6-dicarboxylic acid anhydride was used as substrate
35 rather than benzimidazole-5,6-dicarboxylic acid anhydride. After the anhydride opening step, the mixture of regioisomers formed was separated by chromatography (silica 5% methanol and 95% dichloromethane) and the more polar

regioisomer was taken through the subsequent coupling with 1-adamantanemethylamine.

The compound was isolated and tested as its ammonium salt.

5 Found: C, 64.58; H, 6.51; N, 18.01. $C_{37}H_{41}N_5O_3 \cdot 1.5 H_2O$ requires C, 64.71; H, 6.46; N, 18.35%, 1H NMR (d^6 -DMSO) δ 11.5 (1H, s), 10.1 (1H, s), 8.7 (1H, d), 8.6 (1H, s), 8.5 (1H, t), 7.9 (1H, d), 7.7 (2H, s), 7.5 (1H, t), 7.4 -7.2 (7H, m), 6.5 (1H, s), 4.8 (1H, m), 3.5-2.9 (4H, m), 1.9 (3H, s), 1.6 (6H, q), 1.5 (6H, s).

Example 101 6-(1S-(3-tetrazolylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-5-(1-adamantanemethylaminocarbonyl)-indole

15

This was prepared essentially as in example 100 except that the less polar regioisomer following anhydride opening was used as substrate for subsequent transformations. Found: C, 64.74; H, 6.46; N, 18.07. $C_{37}H_{41}N_5O_3 \cdot 1.5 H_2O$ requires C, 64.71; H, 6.46; N, 18.35%, 1H NMR (d^6 -DMSO) δ 11.5 (1H, s), 10.1 (1H, s), 8.8 (1H, d), 8.6 (1H, s), 8.4 (1H, t), 7.9 (2H, m), 7.7 (1H, d), 7.5 (1H, t), 7.4 -7.2 (7H, m), 6.6 (1H, s), 4.8 (1H, m), 3.5-2.9 (4H, m), 1.9 (3H, s), 1.6 (6H, q), 1.5 (6H, s).

25

Example 102 5-(1S-(3-trifluoromethylsulphonylaminophenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole. Mixture of regioisomers at positions 5 and 6

30

This was prepared essentially as in example 93 except that 3-nitroaniline was used in the course of step a instead of 3,5-dinitroaniline. Found: C, 61.42; H, 5.58; N, 9.65. $C_{37}H_{38}F_3N_5O_5S$ requires C, 61.57 H, 5.31; N, 9.70% 1H NMR (d^6 -DMSO) δ 11.7 (1H, br s), 11.5 (1H, s), 10.1 and 10.0 (1H, 2 x s), 8.7 (1H, m), 8.5 (1H, m), 8.1 (1H, m), 7.9 and 7.8 (1H, 2 x s), 7.8 (1H, m), 7.5 (1H, m), 7.4 (6H, m), 7.2-7.0 (2H, m), 6.6 and 6.5 (1H, 2 x s), 4.7 (1H, m), 3.5-2.8 (4H,

35

m), 1.9 (3H, s), 1.7 (6H, q), 1.5 (6H, m).

Example 103 5-(1S-(3,5-dihydroxy-N-(methyl)aminocarbonyl-phenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole. Mixture of regioisomers at positions 5 and 6

This was prepared essentially as in example 24 except that 1S-(3,5-dibenzyloxy-N-(methyl)aminocarbonyl-phenylaminocarbonyl)-2-phenylethylamine was used in step h instead of 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethyl amine and the mixture of regioisomers formed during this step were not separated ¹H NMR (d⁶-DMSO) δ 11.5 (1H, s), 10.1 (1H, s), 8.7 (1H, dd), 8.5 (1H, m), 8.2 (2H, s), 7.9 and 7.7 (1H, 2 x s), 7.6-6.5 (9H, m), 6.5 (1H, s), 4.7 (1H, m), 3.5-2.7 (10H, m), 1.9 (3H, s), 1.6 (6H, m), 1.5 (6H, m).

Example 104 5-(1S-(3,5-ditetrazolylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole

This was prepared essentially as in example 97 except that L-phenylalanine was used in step a instead of L-2-fluorophenylalanine and the regioisomers were separated immediately prior to final deprotection by column chromatography (silica 75% dichloromethane 25% ethyl acetate). The less polar regioisomer was converted to the compound of this example. ¹H NMR (d⁶-DMSO) δ 11.5 (1H, s), 10.4 (1H, s), 8.8 (3H, m), 8.5 (2H, m), 7.7 (1H, s), 7.5 (1H, t), 7.4-7.0 (6H, m), 6.5 (1H, s), 4.8 (1H, m), 3.5-2.9 (4H, m), 1.8 (3H, s), 1.5 (6H, q), 1.3 (6H, s).

The compound was further characterised and tested as the N-methyl-D-glucamine salt

Example 105 6-(1S-(3,5-ditetrazolylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-5-(1-adamantanemethylaminocarbonyl)-indole

This was prepared essentially as in example 104 except that the more polar regioisomer isolated when regioisomers were separated was converted to the title compound. ¹H NMR (d⁶-DMSO) δ 11.5 (1H, s), 10.4 (1H, s), 8.8 (3H, m), 8.5 (2H, m), 7.9 (1H, s), 7.5 (1H, t), 7.4-7.0 (6H, m), 6.6 (1H, s), 4.8 (1H, m), 3.6-2.9 (4H, m), 1.8 (3H, s), 1.5 (6H, q), 1.3 (6H, s).

The compound was further characterised and tested as the N-methyl-D-glucamine salt

Example 106 5-(1S-(3,5-di-(cis-4-phenyl-3,5-dioxacyclohexaneoxycarbonyl)-phenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethyl-aminocarbonyl)-indole.

15

The product of example 24 (100 mg, 0.15 mmol) and cis-4-phenyl-3,5-dioxacyclohexanol (54 mg, 0.3 mmol) were dissolved in dichloromethane (20 ml) and DCCI (69 mg, 0.3 mmol) was added, followed by DMAP. The mixture was stirred overnight at room temperature and filtered to remove the DCU that had formed. Evaporation, followed by column chromatography (silica 50% ethyl acetate and 50% dichloromethane) followed by trituration with hexane and ethanol gave the title compound as a colourless solid (36 mg), ¹H NMR (d⁶-DMSO) δ 11.5 (1H, s), 10.4 (1H, s), 8.9 (2H, m), 8.8 (1H, d), 8.4 (2H, m), 7.8-6.5 (19H, m), 5.7 (2H, s), 5.0 (2H, s), 4.8 (1H, m), 4.3 (8H, q), 3.5-2.8 (4H, m), 1.8 (3H, s), 1.5 (6H, q), 1.4 (6H, m).

Example 107 5-(1S-(3,5-di-(5-indanoloxycarbonyl)-phenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethyl-aminocarbonyl)-indole.

This material was prepared essentially as in example 106 except that 5-indanol was used instead of cis-4-phenyl-3,5-dioxacyclohexanol. Found: C, 73.48; H, 6.22; N, 6.17. C₅₆H₅₄N₄O₇ requires C, 73.52 H, 6.19; N, 6.12% ,¹H NMR (d⁶-DMSO) δ 11.5 (1H, s), 10.3 (1H, s), 9.0 (2H, d), 8.5 (1H,

t), 8.4 (1H, t), 7.8 (1H, d), 7.7-6.5 (15H, m), 4.8 (1H, m), 3.6-2.8 (4H, m), 2.5 (12H, m), 1.8 (3H, s), 1.5 (6H, q), 1.4 (6H, m).

5 Example 108 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-azabicyclo[2.2.2]oct-3-ylmethylaminocarbonyl)-indole

a. 5-(1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-indole-6-carboxylic acid
10

Indole-5,6-dicarboxylic acid anhydride (1.87g, 10.0 mmol) and 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethyl amine (4.96 g, 9.8 mmol) were dissolved in
15 acetonitrile (100 ml) and stirred and heated at reflux for 30 min. After cooling a yellow crystalline solid was formed which was isolated by filtration, washed with acetonitrile and dried to yield the title compound (3.25 g). This was mainly the regioisomer indicated in the title. The mother
20 liquors when evaporated yielded mainly the other regioisomer. This was not used further in this example.

b. 5-(1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-azabicyclo[2.2.2]oct-3-ylmethylaminocarbonyl)-indole
25

This was prepared essentially as in example 79 step b except that the product of step a above was used instead of the product of example 79 step a, and 1-azabicyclo[2.2.2]oct-3-ylmethylamine instead of 1-adamantanemethylamine.
30

c. 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-azabicyclo[2.2.2]oct-3-ylmethylaminocarbonyl)-indole
35

This was prepared essentially as in example 24 step i except that the dibenzyl ester prepared in step b above was used as substrate instead of the product of example 24 step h. ¹H

NMR (d^6 -DMSO) δ 11.5 (1H, s), 10.1 (1H, 2 x s), 8.7 (4H, m), 8.2 (1H, m), 7.7-6.5 (9H, m), 4.8 (1H, m), 3.6-2.7 (10H, m), 2.4-1.5 (6H, m).

- 5 The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 55.61; H, 6.70; N, 9.40. $C_{42}H_{52}N_6O_{12}$ requires C, 55.74; H, 6.68; N, 9.29%

Example 109 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(4-hydroxycyclohexanemethylaminocarbonyl)-indole Isomer 1 (unknown whether hydroxy group is cis or trans to the methylaminocarbonyl group)

- 15 This was prepared essentially as in example 108 except that 4-benzyloxycyclohexanemethylamine was used in step b instead of 1-azabicyclo[2.2.2]oct-3-ylmethylamine and the cis and trans isomers were separated but not assigned at the end of step b the less polar isomer being used in this example, 1H
- 20 NMR (d^6 -DMSO) δ 10.3 (1H, s), 8.7 (3H, m), 8.5 (1H, t), 8.2 (1H, m), 7.7 (1H, s), 7.5-7.2 (7H, m), 6.5 (1H, s), 4.8 (1H, m), 3.7-2.7 (5H, m), 1.5 and 1.4 (9H, m).

- The compound was further characterised and tested as the di-
- 25 N-methyl-D-glucamine salt. Found: C, 53.29; H, 7.02; N, 8.12. $C_{48}H_{68}N_6O_{18} \cdot 3.1 H_2O$ requires C, 52.93; H, 7.03; N, 7.71%

Example 110 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(4-hydroxycyclohexanemethylaminocarbonyl)-indole. Isomer 2 (unknown whether hydroxy group is cis or trans to the methylaminocarbonyl group)

- This was prepared essentially as in example 109 except that the more polar isomer isolated in step b was used as
- 35 substrate in step c instead of the less polar material. 1H NMR (d^6 -DMSO) δ 10.2 (1H, s), 8.7 (3H, m), 8.5 (1H, t), 8.2 (1H, m), 7.7 (1H, s), 7.5 (1H, t), 7.4-7.2 (7H, m), 6.5 (1H, s), 4.8 (1H, m), 3.5-3.0 (5H, m), 1.7-1.0 (9H, m).

The compound was further characterised and tested as the di-N-methyl-D-glucamine salt. Found: C, 51.93; H, 6.87; N, 8.01. $C_{48}H_{68}N_6O_{18} \cdot 4.8 H_2O$ requires C, 52.28 H, 7.08; N, 7.67%

5 Example 111 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-2-methylbenzimidazole

10 a. 2-Methyl-benzimidazole-5,6-dicarboxylic acid anhydride

This was prepared in several steps from 3,4-dimethoxycarbonylacetanilide by nitration with fuming nitric acid, followed by treatment with sulphuric acid to remove the acetyl group selectively. Catalytic hydrogenation, followed
15 by treatment with hot acetic acid gave the benzimidazole skeleton. Saponification followed by anhydride formation by heating of the diacid gave the title compound.

20 b. 5-(1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-2-methyl-benzimidazole-6-carboxylic acid

This was prepared essentially as in example 108 step a except that the product of step a above was used as
25 substrate instead of indole-5,6-dicarboxylic acid anhydride. The isolated filtrate was the pure carboxylic acid.

30 c. 5-(1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-2-methylbenzimidazole

This was prepared essentially as in example 108 step b except that the product of step b above was used as
35 substrate instead of the product of example 108 step a.

d. 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-2-methylbenzimidazole

This was prepared essentially as in example 108 step c except that the product of step c above was used as substrate instead of the product of example 108 step b.¹H NMR (d⁶-DMSO) δ 10.2 (1H, m), 8.8 (1H, d), 8.7 (2H, s), 8.5 (1H, t), 8.2 (1H, s), 7.8 (1H, br s), 7.4 (5H, m), 7.0 (1H, s), 4.8 (1H, m), 3.5 (1H, m), 3.0 (3H, m), 2.5 (3H, s), 1.8 (3H, s), 1.6 (6H, m), 1.4 (6H, s).

The compound was further characterised and tested as the di-
10 N-methyl-D-glucamine salt. Found: C, 55.75; H, 7.05; N, 8.62. C₅₂H₇₃N₇O₁₇.3 H₂O requires C, 55.65 H, 7.10; N, 8.74%

Example 112 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-4-(1-adamantanemethylamino-
15 carbonyl)-benzimidazole. Regioisomer 1 (assignment of regioisomer uncertain)

a. Benzimidazole-4,5-dicarboxylic acid anhydride

20 This was prepared essentially as in example 111 step a except that 3,4-dimethoxycarbonyl-2-nitroaniline was used instead of 3,4-dimethoxycarbonyl-6-nitroaniline and formic acid was used instead of acetic acid in the course of formation of the second ring. 3,4-dimethoxycarbonyl-2-
25 nitroaniline was isolated as a more minor product during the course of the hydrogenation described in example 111 step a.

b. 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-4-(1-adamantanemethylamino-
30 carbonyl)-benzimidazole

This was prepared essentially as described in example 111 steps b to d except that benzimidazole-4,5-dicarboxylic acid anhydride was used in step b instead of benzimidazole-5,6-
35 dicarboxylic acid anhydride. The two regioisomers formed during the course of these reactions were separated at the end of step c by column chromatography (silica 5% methanol and 95% dichloromethane) with the less polar regioisomer

being taken through and designated as the compound of this example. ¹H NMR (d⁶-DMSO) δ 13.0 (1H, br s), 10.5 (2H, m), 8.6 (4H, m), 8.2 (1H, s), 7.9-7.1 (7H, m), 6.6 (1H, m), 4.8 (1H, m), 3.6-3.0 (4H, m), 1.9 (3H, s), 1.6 (12H, m).

5

The compound was further characterised and tested as the di-N-methyl-D-glucamine salt. Found: C, 55.29; H, 6.98; N, 8.93. C₅₁H₇₁N₇O₁₇·3 H₂O requires C, 55.28 H, 7.00; N, 8.85%

10 Example 113 4-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-5-(1-adamantanemethylamino-carbonyl)-benzimidazole. Regioisomer 2 (assignment of regioisomer uncertain)

15 The material was prepared essentially as in example 112 except that the more polar regioisomer isolated after chromatography was used in the final deprotection step, ¹H NMR (d⁶-DMSO) δ 13.0 (2H, br s), 10.7 and 9.5 (1H, 2 x s), 8.6 (4H, m), 8.2 (1H, s), 7.7 (1H, br s), 7.4 (1H, m), 7.3
20 (6H, m), 4.8 (1H, m), 3.6 (1H, m), 3.0 (2H, m), 1.9 (3H, s), 1.6 (6H, m), 1.4 (6H, s).

The compound was further characterised and tested as the di-N-methyl-D-glucamine salt. Found: C, 56.22; H, 7.00; N, 9.03. C₅₁H₇₁N₇O₁₇·2 H₂O requires C, 56.18 H, 6.93; N, 8.99%

25

Example 114 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylamino-carbonyl)-2-n-butylbenzimidazole

30

This was prepared essentially as in example 111 except that n-pentanoic acid was used in step a instead of acetic acid, ¹H NMR (d⁶-DMSO) δ 13.0 (3H, m), 10.2 (1H, s), 8.8 (1H, d), 8.7 (2H, s), 8.5 (1H, t), 8.2 (1H, s), 7.8 (1H, br s), 7.3
35 (5H, m), 7.0 (1H, s), 4.8 (1H, m), 3.5-2.7 (6H, m), 1.8-1.3 (19H, m), 0.9 (3H, t).

The compound was further characterised and tested as the di-

N-methyl-D-glucamine salt. Found: C, 57.39; H, 7.62; N, 8.59. $C_{55}H_{79}N_7O_{17} \cdot 2 H_2O$ requires C, 57.63 H, 7.30; N, 8.55%

Example 115 2-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-3-(1-adamantanemethylaminocarbonyl)-5-aminonaphthalene. Regioisomer 1 (regiochemistry unassigned)

This was prepared essentially as in example 24 steps g to i except that 5-nitronaphthalene-2,3-dicarboxylic acid anhydride was used as substrate instead of indole-5,6-dicarboxylic acid anhydride. The less polar regioisomer isolated at the penultimate stage was used to prepare the compound of this example. The final deprotection also served to reduce the nitro group, 1H NMR (d^6 -DMSO) δ 13.5 (2H, br s), 10.2 (1H, s), 8.8 (1H, d), 8.7 (2H, d), 8.5 (1H, t), 8.2 (1H, d), 8.0-6.8 (10H, m), 5.7 (2H, br s), 4.8 (1H, m), 3.6-2.9 (4H, m), 1.9 -1.5 (15H, m).

The compound was further characterised and tested as the di-N-methyl-D-glucamine salt. Found: C, 56.90; H, 7.14; N, 7.42. $C_{54}H_{74}N_7O_{17} \cdot 3.3 H_2O$ requires C, 56.94 H, 7.14; N, 7.38%

Example 116 3-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenyl ethylaminocarbonyl)-2-(1-adamantanemethylaminocarbonyl)-5-aminonaphthalene. Regioisomer 2 (opposite regiochemistry to example 115)

This was prepared essentially as in example 115 except that the more polar regioisomer was taken through the final step 1H NMR (d^6 -DMSO) δ 13.5 (2H, br s), 10.2 (1H, s), 8.9 (1H, d), 8.7 (2H, s), 8.4 (2H, m), 8.2-6.8 (10H, m), 5.9 (2H, br s), 4.8 (1H, m), 3.5-2.8 (4H, m), 1.8 -1.5 (15H, m).

The compound was further characterised and tested as the di-N-methyl-D-glucamine salt. Found: C, 51.21; H, 7.26; N, 6.76. $C_{54}H_{74}N_7O_{17} \cdot 10 H_2O$ requires C, 51.51 H, 7.52 N, 6.67%

Example 117 5-(1S-(3,5-diaminocarbonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

- 5 This was prepared essentially as in example 25 except that 1S-(3,5-diaminocarbonyl-phenylaminocarbonyl)-2-phenylethylamine was used in step d instead of 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethyl amine and no final deprotection was required, Found: C, 54.67; H, 5.72; N, 12.58. $C_{37}H_{39}N_7O_5 \cdot 2.2 CH_2Cl_2 \cdot 1.8 DMF$ requires C, 54.65 H, 5.76 N, 12.78% 1H NMR (d^6 -DMSO) δ 12.8 (1H, br s), 10.2 (1H, s), 8.8 (1H, d), 8.5 (1H, t), 8.4 (2H, m), 8.1-7.9 (5H, m), 7.4-7.1 (8H, m), 4.8 (1H, m), 3.4 (2H, m), 2.9 (2H, m), 1.8 (3H, s), 1.4 (6H, m), 1.3 (6H, m).

15

Example 118 5-(1S-(3,5-dihydroxyiminomethylenephenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

- 20 This was prepared essentially as in example 25 except that 1S-(3,5-dihydroxyiminomethylenephenylaminocarbonyl)-2-phenyl ethylamine was used in step d instead of 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethyl amine and no final deprotection was required, Found: C, 63.18; H, 6.18; N, 14.01. $C_{37}H_{39}N_7O_5 \cdot 2.3 H_2O$ requires C, 63.25 H, 6.25 N, 13.95% 1H NMR (d^6 -DMSO) δ 12.8 (1H, br s), 11.3 (2H, s), 10.0 (1H, m), 8.8 (1H, d), 8.6 (1H, t), 8.4 (1H, s), 8.1 (4H, m), 7.9 (1H, m), 7.5 (1H, s), 7.3 (5H, m), 7.2 (1H, m), 4.8 (1H, m), 3.5 (1H, m), 3.1-2.8 (3H, m), 1.8 (3H, s), 1.5 (6H, m), 1.4 (6H, m).

30

Example 119 5-(1S-(3,5-dihydroxymethylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

35

- a. 5-(1S-(3,5-dihydroxymethylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole diacetoxycarbonate derivative.

This was prepared essentially as example 79 except that the diacetoxycarbonate derivative of 1S-(3,5-dihydroxymethylphenylaminocarbonyl)-2-phenylethylamine was used instead of 1S-(3-benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine in step a.

b. 5-(1S-(3,5-dihydroxymethylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

10

The product of step a above (1.91 g, 2.5 mmol) was dissolved in methanol (210 ml) and was treated with a 1% solution of potassium carbonate in water (105 ml). After stirring overnight, the methanol was removed by evaporation and the resulting solid extracted with ethyl acetate. The organic layer was washed with brine, dried, filtered and evaporated to leave the title compound, Found: C, 69.69; H, 6.61; N, 11.19. $C_{37}H_{41}N_3O_8$ requires C, 69.90 H, 6.50 N, 11.02% 1H NMR (d^6 -DMSO) δ 12.8 (1H, br s), 9.8 (1H, s), 8.8 (1H, d), 8.5 (1H, t), 8.4 (1H, s), 7.9 (1H, m), 7.7 (2H, s), 7.3 (5H, m), 7.1 (1H, s), 7.0 (1H, s), 5.2 (2H, t), 4.7 (1H, m), 4.5 (4H, d), 3.3 (2H, m), 2.9 (2H, m), 1.9 (3H, s), 1.6 (6H, m), 1.5 (6H, m).

25 Example 120 5-(1S-(3,5-hydroxycarbonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

The compound of example 119 was oxidised by treatment with oxalyl chloride in DMSO and triethylamine using dichloromethane as solvent, following the Swern oxidation protocol in 45% yield, Found: C, 67.23; H, 6.08; N, 10.41. $C_{37}H_{37}N_3O_5 \cdot 1.7 H_2O$ requires C, 67.13 H, 6.15 N, 10.58% 1H NMR (d^6 -DMSO) δ 12.8 (1H, br s), 10.3 (1H, s), 10.1 (2H, s), 8.9 (1H, d), 8.7 (2H, s), 8.6 (1H, t), 8.4 (1H, s), 8.2 (1H, s), 7.8 (1H, s), 7.4 (5H, m), 7.1 (1H, s), 4.8 (1H, m), 3.3 (2H, m), 3.0 (2H, m), 2.0 (3H, s), 1.6 (6H, m), 1.4 (6H, m).

Example 121 5-(1S-(3,5-di-t-butylcarbonyloxymethyloxy-carbonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzofuran. Mixture of regioisomers at positions 5 and 6

5

a. 3,4-dimethoxycarbonyl-2-iodophenol

The dimethyl ester of 4-hydroxyphthallic acid (4.20 g, 20 mmol), was dissolved in triflic acid (15 g, 100 mmol), and
10 cooled to 0°C. N-iodosuccinimide (4.5 g, 20 mmol) was added portionwise and stirred at room temperature for 2h. The reaction mixture was poured onto a mixture of ice and water and the aqueous layer was extracted with dichloromethane (3 x 75 ml). The combined organic layers were washed
15 successively with 5% sodium bisulphite solution and brine before being dried, filtered and evaporated, to yield the title compound 4.51 g.

20

b. 5,6-Dimethoxycarbonyl-2-trimethylsilyl-benzofuran

The product of step a (4.5 g, 13.4 mmol) and TMS-acetylene (1.71 g, 17.4 mmol) in triethylamine (50 ml) and dioxan (80 ml) was degassed with argon for 15 min. Copper I iodide (152 mg, 0.8 mmol), was added followed by bis triphenylphosphine
25 palladium dichloride. (564 mg, 0.8 mmol). The reaction was stirred at 60°C overnight under an atmosphere of argon. The solvents were removed by evaporation and the resulting oil was redissolved in dichloromethane and washed sequentially with 10% citric acid solution and brine. The organic layer
30 was dried, filtered and evaporated and passed through a short silica column to give the title compound.

c. Benzofuran-5,6-dicarboxylic acid anhydride

35 This was prepared from the product of step b in several steps by treatment with hydrogen fluoride/pyridine complex to remove the silicon group, followed by saponification to generate the diacid. Anhydride ring formation occurred on

heating the diacid to approximately 100°C.

- d. 6-(1-adamantanemethylaminocarbonyl)-benzofuran-5-carboxylic acid. Mixture of regioisomers at positions 5 and 6

This was prepared essentially as in example 24 step g except that benzofuran-5,6-dicarboxylic acid anhydride was used as substrate instead of indole-5,6-dicarboxylic acid anhydride.

10

- e. 5-(1S-(3,5-di-t-butylcarbonyloxymethyloxycarbonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzofuran. Mixture of regioisomers at positions 5 and 6

This was prepared essentially as in example 24 step h except that 6-(1-adamantanemethylaminocarbonyl)-benzofuran-5-carboxylic acid was used instead of 6-(1-adamantanemethylaminocarbonyl)-indole-5-carboxylic acid and 1S-(3,5-di-t-butylcarbonyloxymethyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine was used instead of 1S-(3,5-di-benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine. No attempt was made to separate the regioisomers at this point, ¹H NMR (d⁶-DMSO) δ 10.2 (1H, s), 9.0 (1H, d), 8.8 (2H, s), 8.6 (1H, t), 8.2 (2H, m), 7.9 (1H, 2 x s), 7.3 (5H, m), 7.1 (2H, m), 6.0 (4H, s), 4.7 (1H, m), 3.4 (2H, m), 2.9 (2H, m), 1.4-1.3 (15H, m), 1.2 (18H, s).

- 30 Example 122 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzofuran. Mixture of regioisomers at positions 5 and 6

- 35 a. 5-(1S-(3,5-di-allyloxycarbonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzofuran. Mixture of regioisomers at positions 5 and 6

This was prepared essentially as in example 121 except that 1S-(3,5-di-allyloxycarbonylphenylaminocarbonyl)-2-phenylethyl amine was used in step e instead of 1S-(3,5-di-
5 butylcarbonyloxymethyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine

b. 5-(1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylamino-
carbonyl)-benzofuran

10

The product of step a above was de-esterified by treatment with diethylamine in THF in the presence of palladium tetrakis triphenylphosphine. The product was initially isolated as the bis diethylamine salt, ¹H NMR (d⁶-DMSO) δ
15 10.2 (1H, s), 9.0 (1H, d), 8.8 (2H, s), 8.4 (3H, m), 8.1 (2H, m), 7.9 (1H, 2 x s), 7.4-7.1 (6H, m), 7.0 (1H, m), 4.7 (1H, m), 3.4 (1H, m), 2.9 (3H, m), 1.8 (3H, s), 1.5 (6H, q), 1.3 (6H, s).

20 The compound was further characterised and tested as the di-N-methyl-D-glucamine salt. Found: C, 69.29; H, 6.05 N, 5.86. C₅₂H₇₁N₅O₁₈ requires C, 69.45; H, 5.97; N, 6.07%

Example 123 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylamino-
25 carbonyl)-2,3-dihydro-benzofuran. Mixture of regioisomers at positions 5 and 6

This was prepared by hydrogenation of the dibenzyl ester of
30 the compound of example 122 using 10% palladium on charcoal as catalyst. ¹H NMR (d⁶-DMSO) δ 10.1 (1H, 2 x s), 8.8 and 8.7 (1H, m), 8.5 (2H, m), 8.2 (2H, m), 7.5-7.2 (6H, m), 6.9 (1H, m), 4.7 (1H, m), 4.6 (2H, m), 3.4 (2H, m), 3.0 (4H, m), 1.8 (3H, s), 1.5 (6H, m), 1.4 (6H, s).

35

The compound was further characterised and tested as the di-N-methyl-D-glucamine salt. Found: C, 55.84; H, 6.99; N, 6.61. C₅₂H₇₁N₅O₁₈ .3.0 H₂O requires C, 56.16; H, 7.18; N, 6.30%

Example 124 5-(1S-(3,5-dimethoxycarbonylphenylamino-carbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzofuran

5 This was prepared by treatment of the compound of example 121 with ammonia in methanol, ¹H NMR (d⁶-DMSO) δ 10.2 (1H, m), 8.9 (1H, m), 8.8 (2H, s), 8.2 (2H, m), 8.0 (1H, s), 7.9 (1H, 2 x s), 7.4-7.0 (7H, m), 4.7 (1H, m), 3.9 (6H, s), 3.4-2.9 (4H, m), 1.9 (3H, s), 1.5 (6H, q), 1.4 (6H, s).

10

Example 125 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzothiophene. Mixture of regioisomers at positions 5 and 6

15

a. Benzothiophene-5,6-dicarboxylic acid anhydride

This was prepared in several steps starting from 3-methyl-2-carboxy-thiophene. Esterification and allylic bromination
20 gave a material which on treatment with the sodium salt of 4-toluenesulphonic acid gave 3-toluenesulphonylmethyl-2-methoxycarbonyl-thiophene. The methyl ester was reduced with superhydride and the resulting alcohol oxidised to the aldehyde using PDC. Cycloaddition with dimethyl fumarate
25 using potassium t-butoxide as base gave benzothiophene-5,6-dicarboxylic acid. This was converted to the title compound by treatment with acetic anhydride.

b. 5-(1S-(3,5-di-t-butyloxycarbonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzothiophene.
30

This was prepared essentially as in example 121 steps d and e except that benzothiophene-5,6-dicarboxylic acid anhydride
35 was used in step d instead of benzofuran-5,6-dicarboxylic acid anhydride and 1S-(3,5-di-t-butyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine was used in step e instead of 1S-(3,5-di-t-butylcarbonyloxymethyloxycarbonylphenyl-

aminocarbonyl)-2-phenylethylamine.

- c. 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-5 benzothiophene

- The product of step b was treated with trifluoroacetic acid for 2h. The volatile material was removed by evaporation and the residue azeotroped several times with diethyl ether to
- 10 leave the title compound, ¹H NMR (d⁶-DMSO) δ 13.2 (2H, br s), 10.2 (1H, s), 8.9 (1H, m), 8.7 (2H, m), 8.4 (1H, m), 8.3 (2H, m), 8.2 (2H, m), 8.0 (1H, m), 7.5-7.0 (5H, m), 4.8 (1H, m), 3.3-2.9 (4H, m), 1.8 (3H, s), 1.6 (6H, q), 1.4 (6H, s).
- 15 The compound was further characterised and tested as the di-N-methyl-D-glucamine salt

- Example 126 (±)-6-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-5-(1-adamantanemethylaminocarbonyl)-4,5,6,7-tetrahydro-5-aza-benzimidazole.
- 20

a. (±)-N-1,5-di-t-Butyloxycarbonyl-6-carboxy-4,5,6,7-tetrahydro-5-aza-benzimidazole

- 25 This was prepared by treatment of D/L-histidine with aqueous formaldehyde using standard Pictet-Spengler conditions. The product was treated with BOC anhydride to give the title compound.

- 30 b (±)-N-1,5-di-t-Butyloxycarbonyl-6-(1S-(3,5-di-benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-4,5,6,7-tetrahydro-5-aza-benzimidazole

- This was prepared by treatment of the product of step a with
- 35 one equivalent of 1S-(3,5-di-benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine and 1.2 equivalents of DCCI. The product was isolated by filtration, evaporation and column chromatography (silica, ethyl acetate: DCM 1:2).

c (±)-6-(1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-5-(1-adamantanemethylaminocarbonyl)-4,5,6,7-tetrahydro-5-aza-benzimidazole

5 This was prepared by treating the product of step b with TFA and then with one equivalent of 1-adamantanemethylisocyanate in the presence of DMAP. After stirring overnight the reaction mixture was evaporated to dryness and the residue chromatographed (silica, acetone:toluene 1:2). The most
10 polar product was the title compound.

d. (±)-6-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-5-(1-adamantanemethylaminocarbonyl)-4,5,6,7-tetrahydro-5-aza-benzimidazole.

15

This was prepared essentially as in example 24 step i except that the dibenzyl ester prepared above was used as substrate instead of the product of example 24 step h, ¹H NMR (d⁶-DMSO) δ 10.3 (1H, m), 8.4 (2H, m), 8.2 (1H, s), 8.0-7.7 (1H, m),
20 7.4 (1H, m), 7.2 (6H, m), 6.5 (1H, m), 5.1 (1H, m), 4.5 (1H, m), 4.2 (1H, m), 3.3-2.8 (6H, m), 1.8 (3H, m), 1.6 (6H, q), 1.4 (6H, m).

The compound was further characterised and tested as the di-
25 N-methyl-D-glucamine salt. Found: C, 53.86; H, 7.40; N, 9.53. C₅₀H₇₄N₈O₁₇ .3.5 H₂O requires C, 53.91 H, 7.28; N, 9.98%

Example 127 5-(1S-(2-chloro-5-carboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole
30

This was prepared essentially as in example 25 except that 1S-(2-chloro-5-benzyloxycarbonylphenylaminocarbonyl)-2-phenyl ethylamine was used in step d instead of 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine.
35 1S-(2-chloro-5-benzyloxycarbonylphenylaminocarbonyl)-2-phenyl ethylamine was prepared by coupling BOC-L-

phenylalanine with 2-chloro-5-benzyloxycarbonylaniline using PyBrOP, followed by treatment with trifluoroacetic acid, ¹H NMR (d⁶-DMSO) δ 13.2 (1H, br s), 12.8 (1H, br s), 10.0 (1H, s), 8.9 (1H, d), 8.4 (2H, s), 8.2 (1H, s), 8.0-7.6 (3H, m), 7.4-7.1 (6H, m), 4.8 (1H, m), 3.4 (1H, m), 2.9 (3H, m), 1.8 (3H, s), 1.6 (6H, q), 1.4 (6H, s).

The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 58.33; H, 6.49; N, 9.09.
10 C₄₃H₅₃ClN₆O₁₀ .2.3 H₂O requires C, 58.01 H, 6.51; N, 9.44%

Example 128 5-(1S-(3-trifluoroacetylaminosulphonylphenyl)-aminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole
15

This was prepared essentially as in example 99 except that the product of example 25 step c was used in step b instead of the product of example 24 step g, Found: C, 55.01; H, 5.27; N, 10.33. C₃₇H₃₇F₃N₆O₆S .2.3 H₂O requires C, 58.01 H, 6.51; N, 9.44% ¹H NMR (d⁶-DMSO) δ 10.1 (1H, s), 8.9 (1H, d), 8.5 (5H, m), 8.0-7.0 (10H, m), 4.8 (1H, m), 3.6-2.9 (4H, m), 1.9 (3H, s), 1.6 (6H, m), 1.5 (6H, m).

25 Example 129 5-(3S-(3,5-dicarboxyphenylaminocarbonyl)-1,2,3,4-tetrahydroisoquinolino-2-carbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

This was prepared essentially as in example 79 except that 30 3S-(3,5-dibenzyloxyphenylaminocarbonyl)-1,2,3,4-tetrahydroisoquinoline was used as substrate instead of 1S-(3-benzyloxycarbonylphenyl-aminocarbonyl)-2-phenylethylamine in step a. The 3S-(3,5-dibenzyloxyphenylaminocarbonyl)-1,2,3,4-tetrahydroisoquinoline was prepared by coupling BOC-35 3S-carboxy-1,2,3,4-tetrahydroisoquinoline and 3,5-dibenzyloxycarbonylaniline in the presence of PyBROP, followed by treatment with trifluoroacetic acid, ¹H NMR (d⁶-DMSO) δ 13.0 (3H, br s), 11.5 and 10.0 (1H, 2 x s), 9.0-7.0

(11H, m), 5.4 (1H, m), 4.8-4.2 (2H, m), 3.5-2.8 (4H, m), 1.9 (3H, m), 1.5 (6H, m), 1.4 (6H, m).

The compound was further characterised and tested as the di-
5 N-methyl-D-glucamine salt. Found: C, 55.51; H, 6.89 N, 8.80.
C₅₂H₇₁N₇O₁₇ .3.2 H₂O requires C, 55.58 H, 6.94; N, 8.73%

Example 130 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-
phenylethylaminocarbonyl)-6-(2-naphthalenenemethylamino-
10 carbonyl)-benzimidazole

This was prepared essentially as in example 79 except that
1S-(3,5-di-benzyloxycarbonylphenylaminocarbonyl)-2-
phenylethylamine was used in step a instead of 1S-(3-
15 benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine and
2-naphthalenemethylamine was used in step b instead of 1-
adamantanemethylamine, ¹H NMR (d⁶-DMSO) δ 12.9 (1H, br s),
10.1 (1H, s), 9.3 (1H, t), 8.9 (1H, d), 8.7 (2H, s), 8.4
(2H, s), 8.1 (1H, s), 8.0 (1H, m), 7.7 (4H, m), 7.4 (8H, m),
20 4.8 (3H, m), 3.0 (2H, m).

The compound was further characterised and tested as the di-
N-methyl-D-glucamine salt. Found: C, 54.92; H, 6.35 N, 8.95.
C₅₁H₆₃N₇O₁₇ .3.7 H₂O requires C, 55.06 H, 6.38; N, 8.81%

25

Example 131 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-(3-
fluorophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylamino-
carbonyl)-benzimidazole

30 This was prepared essentially as in example 79 except that
1S-(3,5-di-benzyloxycarbonylphenylaminocarbonyl)-2-(3-
fluorophenyl)ethylamine was used in step a instead of 1S-(3-
benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine.
The 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-(3-
35 fluorophenyl)ethylamine was prepared by coupling BOC-L-3-
fluorophenylalanine and 3,5-dibenzyloxycarbonylaniline in
the presence of PyBROP, followed by treatment with
trifluoroacetic acid, ¹H NMR (d⁶-DMSO) δ 13.0 (3H, br s),

10.2 (1H, s), 8.9 (1H, d), 8.7 (2H, s), 8.5 (1H, t), 8.4 (1H, s), 8.2 (1H, s), 7.9 (1H, s), 7.4 (1H, m), 7.2 (4H, m), 4.8 (1H, m), 3.6-2.9 (4H, m), 1.8 (3H, s), 1.7 (6H, q), 1.5 (6H, s).

5

The compound was further characterised and tested as the di-
N-methyl-D-glucamine salt

Example 132 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-(4-
10 fluorophenyl)ethylaminocarbonyl)-6-(1-adamantanemethyl-
aminocarbonyl)-benzimidazole

This was prepared essentially as in example 79 except that
1S-(3,5-di-benzyloxycarbonylphenylaminocarbonyl)-2-(4-
15 fluorophenyl)ethylamine was used in step a instead of 1S-(3-
benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine.
The 1S-(3,5-di-benzyloxycarbonylphenylaminocarbonyl)-2-(4-
fluorophenyl)ethylamine was prepared by coupling BOC-L-4-
fluorophenylalanine and 3,5-dibenzyloxycarbonylaniline in
20 the presence of PyBROP, followed by treatment with
trifluoroacetic acid, ¹H NMR (d⁶-DMSO) δ 13.0 (3H, br s),
10.2 (1H, s), 8.9 (1H, d), 8.7 (2H, s), 8.5 (1H, t), 8.4
(1H, s), 8.2 (1H, s), 7.9 (1H, s), 7.4 (2H, m), 7.2 (3H, m),
4.8 (1H, m), 3.6-2.9 (4H, m), 1.8 (3H, s), 1.7 (6H, q), 1.5
25 (6H, s).

The compound was further characterised and tested as the di-
N-methyl-D-glucamine salt

Example 133 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-(2-
30 trifluoromethylphenyl)ethylaminocarbonyl)-6-(1-
adamantanemethylaminocarbonyl)-benzimidazole

This was prepared essentially as in example 79 except that
35 1S-(3,5-di-benzyloxycarbonylphenylaminocarbonyl)-2-(2-
trifluoromethylphenyl)ethylamine was used in step a instead
of 1S-(3-benzyloxycarbonylphenylaminocarbonyl)-2-phenyl-
ethylamine. The 1S-(3,5-di-benzyloxycarbonylphenylamino-

carbonyl)-2-(2-trifluoromethylphenyl)-ethylamine was prepared by coupling BOC-L-2-trifluoromethylphenylalanine and 3,5-dibenzoyloxycarbonylaniline in the presence of PyBROP, followed by treatment with trifluoroacetic acid, ¹H NMR (d⁶-DMSO) δ 13.0 (3H, br s), 10.2 (1H, s), 9.0 (1H, d), 8.7 (2H, s), 8.6 (1H, t), 8.4 (1H, s), 8.2 (1H, s), 7.9 (1H, s), 7.7 (4H, m), 7.2 (1H, m), 4.9 (1H, m), 3.8-3.0 (4H, m), 1.8 (3H, s), 1.6 (6H, q), 1.5 (6H, s).

10 The compound was further characterised and tested as the di-N-methyl-D-glucamine salt Found: C, 52.67; H, 6.57; N, 8.25. C₅₂H₇₀F₃N₇O₁₇ .3.5 H₂O requires C, 52.70 H, 6.55; N, 8.27%

15 Example 134 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-(4-iodophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

a 5-(1S-(3,5-di-allyloxyphenylaminocarbonyl)-2-(4-iodophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

This was prepared essentially as in example 79 steps a and b except that 1S-(3,5-di-allyloxycarbonylphenylaminocarbonyl)-2-(4-iodophenyl)ethylamine was used in step a instead of 1S-(3-benzoyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine. The 1S-(3,5-di-allyloxycarbonylphenylaminocarbonyl)-2-(4-iodophenyl)ethylamine was prepared by coupling BOC-L-4-iodophenylalanine and 3,5-diallyloxycarbonylaniline in the presence of PyBROP, followed by treatment with trifluoroacetic acid.

b 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-(4-iodophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

This was prepared essentially as in example 122 step b but using the product of step a above as substrate instead of 5-

(1S-(3,5-di-allyloxycarbonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzofuran. The compound was isolated and characterised as a bis diethylamine salt ^1H NMR (d^6 -DMSO) δ 10.1 (1H, s), 8.8 (1H, d), 8.4 (4H, s), 8.2 (1H, s), 7.9 (1H, s), 7.7 (2H, m), 7.3 (1H, m), 7.2 (2H, m), 4.7 (1H, m), 3.5-2.9 (4H, m), 1.8 (3H, s), 1.7 (6H, q), 1.5 (6H, s).

Example 135 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-(2-chlorophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

This was prepared essentially as in example 134 except that 1S-(3,5-di-allyloxycarbonylphenylaminocarbonyl)-2-(2-chlorophenyl)ethylamine instead of 1S-(3,5-di-allyloxycarbonylphenylaminocarbonyl)-2-(4-iodophenyl)ethylamine in step a. The 1S-(3,5-di-allyloxycarbonylphenylaminocarbonyl)-2-(2-chlorophenyl)ethylamine was prepared by coupling BOC-L-2-chlorophenylalanine and 3,5-diallyloxycarbonylaniline in the presence of PyBROP, followed by treatment with trifluoroacetic acid. The title compound was isolated and characterised as a bis diethylamine salt. Found: C, 62.21; H, 7.05; N, 11.22. $\text{C}_{45}\text{H}_{58}\text{ClN}_7\text{O}_7 \cdot 1.5 \text{ H}_2\text{O}$ requires C, 62.02 H, 7.06; N, 11.25% ^1H NMR (d^6 -DMSO) δ 10.1 (1H, s), 8.8 (1H, d), 8.5 (3H, s), 8.4 (1H, s), 8.2 (1H, s), 7.9 (1H, s), 7.5-7.2 (7H, m), 4.8 (1H, m), 3.6-2.9 (4H, m), 1.8 (3H, s), 1.6 (6H, q), 1.5 (6H, s).

Example 136 (\pm)-5-(1-(3,5-dicarboxyphenylaminocarbonyl)-2-pentafluorophenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

This was prepared essentially as in example 79 except that (\pm)-1-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-pentafluorophenylethylamine was used in step a instead of 1S-(3-benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine. (\pm)-1-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-pentafluorophenylethylamine was prepared by coupling BOC-

pentafluorophenylalanine with 3,5-dibenzyloxycarbonylaniline using PyBrOP, followed by treatment with trifluoroacetic acid, ¹H NMR (d⁶-DMSO) δ 13.0 (2H, br s), 10.2 (1H, s), 8.9 (1H, d), 8.6 (2H, d), 8.5 (1H, t), 8.4 (1H, s), 8.2 (1H, d), 7.9 (1H, s), 7.4 (1H, s), 4.8 (1H, m), 3.5 (1H, dd), 3.2 (1H, dd), 3.0 (2H, d), 1.9 (3H, s), 1.5 (6H, q), 1.4 (6H, s).

The compound was further characterised and tested as the di-
 10 N-methyl-D-glucamine salt. Found: C, 50.83; H, 6.04; N, 8.17. C₅₁H₆₆F₅N₇O₁₇ · 3.3H₂O requires C, 50.87; H, 6.08; N, 8.14%

Example 137 5-(1S-(3-acetylaminosulphonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole
 15

a 1S-(3-acetylaminosulphonylphenylaminocarbonyl)-2-phenylethylamine
 20

This was prepared as in example 99 step a except that acetic anhydride was used to acylate the sulphonamide instead of trifluoroacetic anhydride.

25 b. 5-(1S-(3-acetylaminosulphonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

This was prepared essentially as in example 128 except that
 30 the product of step a above was used as substrate instead of 1S-(3-trifluoroacetylaminosulphonylphenylaminocarbonyl)-2-phenylethylamine in step b, ¹H NMR (d⁶-DMSO) δ 12.1 (1H, br s), 10.2 (1H, s), 8.9 (1H, d), 8.6 (3H, m), 8.0-7.2 (10H, m), 4.8 (1H, m), 3.6-2.9 (4H, m), 1.9 (6H, m), 1.6 (6H, m),
 35 1.5 (6H, m).

Example 138 5-(1S-(3-acetylaminosulphonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

methylaminocarbonyl)-indole. Mixture of regioisomers at positions 5 and 6

This was prepared essentially as in example 99 except that
5 1S-(3-acetylaminosulphonylphenylaminocarbonyl)-2-phenylethylamine was used in step b instead of 1S-(3-trifluoroacetylaminosulphonylphenylaminocarbonyl)-2-phenylethylamine,
¹H NMR (d⁶-DMSO) δ 12.1 (1H, br s), 11.5 (1H, s), 10.3 (1H, 2 x s), 8.8 (1H, 2 x d), 8.7-7.2 (13H, m), 6.6 and 6.5 (1H, 10 m), 4.8 (1H, m), 3.6-2.8 (4H, m), 1.9 (6H, m), 1.6 (6H, m), 1.5 (6H, m).

Example 139 5-(1S-(3-benzoylamino-sulphonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole
15

This was prepared essentially as in example 137 except that benzoyl chloride was used as acylating agent during the course of step a instead of acetic anhydride, ¹H NMR (d⁶-
20 DMSO) δ 12.8 (1H, br s), 10.1 (1H, s), 8.8 (1H, d), 8.5 (3H, m), 8.3-7.2 (16H, m), 4.8 (1H, m), 3.6-2.9 (4H, m), 1.9 (3H, m), 1.6 (6H, m), 1.5 (6H, m).

Example 140 5-(1S-(2-methoxy-5-carboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole
25

This was prepared essentially as in example 79 except that 1S-(2-methoxy-5-benzyloxycarbonylphenylaminocarbonyl)-2-
30 phenylethylamine was used in step a instead of 1S-(3-benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine. The 1S-(2-methoxy-5-benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine was prepared by coupling BOC-L-phenylalanine and 2-methoxy-5-benzyloxycarbonylaniline in the
35 presence of PyBROP, followed by treatment with trifluoroacetic acid, ¹H NMR (d⁶-DMSO) δ 12.7 (2H, br s), 9.4 (1H, s), 8.8 (1H, d), 8.5 (1H, s), 8.4 (1H, s), 8.2 (1H, t), 7.7 (2H, m), 7.3 (7H, m), 4.8 (1H, m), 3.9 (3H, s), 3.4-2.8 (4H, m),

1.9 (3H, s), 1.6 (6H, q), 1.4 (6H, s).

The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 59.15; H, 7.00; N, 9.41.

5 C₄₄H₅₆N₆O₁₁.2.75 H₂O requires C, 59.08 H, 6.93; N, 9.40%

Example 141 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(2-naphthalenenemethylaminocarbonyl)-indole. Mixture of regioisomers at positions 5 and

10 6

This compound was prepared essentially as in example 130 except that indole-5,6-dicarboxylic acid anhydride was used in step a instead of benzimidazole-5,6-dicarboxylic acid
15 anhydride ¹H NMR (d⁶-DMSO) δ 11.6 (1H, br s), 10.2 (1H, s), 9.3 (1H, t), 8.8 (1H, d), 8.7 (2H, s), 8.4 (2H, s), 8.1 (1H, s), 7.8 (4H, m), 7.6-7.2 (11H, m), 6.5 (1H, s), 4.8 (3H, m), 3.5 (1H, dd), 3.0 (1H, dd).

20 The compound was further characterised and tested as the di-N-methyl-D-glucamine salt

Example 142 (±)- 5-(1-(3,5-dicarboxyphenylaminocarbonyl)-2-(2,6-difluorophenyl)ethylaminocarbonyl)-6-(1-adamantane-
25 methylaminocarbonyl)-benzimidazole

This was prepared essentially as in example 79 except that (±)-1-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-(2,6-difluorophenyl)ethylamine was used in step a instead of 1S-
30 (3-benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine. (±)-1-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-(2,6-difluorophenyl)ethylamine was prepared by coupling BOC-2,6-difluorophenylalanine with 3,5-dibenzyloxycarbonylaniline using PyBrOP, followed by treatment with trifluoroacetic
35 acid, ¹H NMR (d⁶-DMSO) δ 13.3 (2H, br s), 12.9 (1H, br s), 10.2 (1H, s), 8.9 (1H, d), 8.7 (2H, d), 8.6 (1H, t), 8.4 (1H, s), 8.2 (1H, d), 7.9 (1H, m), 7.4 (1H, m), 7.3 (1H, m), 7.1 (2H, m), 4.8 (1H, m), 3.5 (1H, dd), 3.1 (1H, dd),

2.9 (2H, d), 1.9 (3H, s), 1.6 (6H, m), 1.5 (6H, s).

The compound was further characterised and tested as the di-
N-methyl-D-glucamine salt

5

Example 143 5-(1R-(3,5-dicarboxyphenylaminocarbonyl)-2-(2-fluorophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

- 10 This was prepared essentially as in example 79 except that 1R-(3,5-di-benzyloxycarbonylphenylaminocarbonyl)-2-(2-fluorophenyl)ethylamine was used in step a instead of 1S-(3-benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine. The 1R-(3,5-di-benzyloxycarbonylphenylaminocarbonyl)-2-(2-
15 fluorophenyl)ethylamine was prepared by coupling BOC-D-2-fluorophenylalanine and 3,5-dibenzyloxycarbonylaniline in the presence of PyBROP, followed by treatment with trifluoroacetic acid, ¹H NMR (d⁶-DMSO) δ 13.0 (3H, br s), 10.2 (1H, s), 8.9 (1H, d), 8.7 (2H, s), 8.6 (1H, t), 8.4
20 (1H, s), 8.2 (1H, s), 7.9 (1H, d), 7.4-7.2 (4H, m), 7.1 (1H, s), 4.8 (1H, m), 3.6-2.9 (4H, m), 1.8 (3H, s), 1.6 (6H, m), 1.3 (6H, m).

The compound was further characterised and tested as the di-
25 N-methyl-D-glucamine salt

Example 144 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-(2,4-difluorophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

30

- This was prepared essentially as in example 79 except that 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-(2,4-difluorophenyl)ethylamine was used in step a instead of 1S-(3-benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine.
35 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-(2,4-difluorophenyl)ethylamine was prepared by coupling BOC-L-2,4-difluorophenylalanine with 3,5-dibenzyloxycarbonylaniline using PyBrOP, followed by treatment with

trifluoroacetic acid, ¹H NMR (d⁶-DMSO) δ 13.2 (3H, br s), 10.2 (1H, s), 8.9 (1H, d), 8.7 (2H, d), 8.6 (1H, t), 8.4 (1H, s), 8.2 (1H, t), 7.5 (1H, m), 7.3 (2H, m), 7.2 (1H, s), 7.1 (1H, m), 4.8 (1H, m), 3.5 (1H, dd), 3.0 (3H, m), 1.9 (3H, s), 1.6 (6H, q), 1.5 (6H, s).

The compound was further characterised and tested as the di-N-methyl-D-glucamine salt

- 10 Example 145 5-(1R-(3,5-dicarboxyphenylaminocarbonyl)-2-(2,4-difluorophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

This was prepared essentially as in example 79 except that
15 1R-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-(2,4-difluorophenyl)ethylamine was used in step a instead of 1S-(3-benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine.
1R-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-(2,4-difluorophenyl)ethylamine was prepared by coupling BOC-D-
20 2,4-difluorophenylalanine with 3,5-dibenzyloxycarbonyl-aniline using PyBrOP, followed by treatment with trifluoroacetic acid, ¹H NMR (d⁶-DMSO) δ 13.2 (3H, br s), 10.2 (1H, s), 8.9 (1H, d), 8.7 (2H, d), 8.6 (1H, t), 8.4 (1H, s), 8.2 (1H, t), 7.5 (1H, m), 7.3 (2H, m), 7.2 (1H, s),
25 7.1 (1H, m), 4.8 (1H, m), 3.5 (1H, dd), 3.0 (3H, m), 1.9 (3H, s), 1.6 (6H, q), 1.5 (6H, s).

The compound was further characterised and tested as the di-N-methyl-D-glucamine salt

30

Example 146 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-(2,6-difluorophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

35 This was prepared essentially as in example 79 except that 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-(2,6-difluorophenyl)ethylamine was used in step a instead of 1S-(3-benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine.

1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-(2,6-difluorophenyl)ethylamine was prepared by coupling BOC-L-2,6-difluorophenylalanine with 3,5-dibenzyloxycarbonylaniline using PyBrOP, followed by treatment with trifluoroacetic acid, ¹H NMR (d⁶-DMSO) δ 13.3 (2H, br s), 12.9 (1H, br s), 10.2 (1H, s), 8.9 (1H, d), 8.7 (2H, d), 8.6 (1H, t), 8.4 (1H, s), 8.2 (1H, d), 7.9 (1H, m), 7.4 (1H, m), 7.3 (1H, m), 7.1 (2H, m), 4.8 (1H, m), 3.5 (1H, dd), 3.1 (1H, dd), 2.9 (2H, d), 1.9 (3H, s), 1.6 (6H, m), 1.5 (6H, s).

10

The compound was further characterised and tested as the di-N-methyl-D-glucamine salt

Example 147 5-(1R-(3,5-dicarboxyphenylaminocarbonyl)-2-(2,6-difluorophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

This was prepared essentially as in example 79 except that 1R-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-(2,6-difluorophenyl)ethylamine was used in step a instead of 1S-(3-benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine. 1R-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-(2,6-difluorophenyl)ethylamine was prepared by coupling BOC-D-2,6-difluorophenylalanine with 3,5-dibenzyloxycarbonylaniline using PyBrOP, followed by treatment with trifluoroacetic acid, ¹H NMR (d⁶-DMSO) δ 13.3 (2H, br s), 12.9 (1H, br s), 10.2 (1H, s), 8.9 (1H, d), 8.7 (2H, d), 8.6 (1H, t), 8.4 (1H, s), 8.2 (1H, d), 7.9 (1H, m), 7.4 (1H, m), 7.3 (1H, m), 7.1 (2H, m), 4.8 (1H, m), 3.5 (1H, dd), 3.1 (1H, dd), 2.9 (2H, d), 1.9 (3H, s), 1.6 (6H, m), 1.5 (6H, s).

The compound was further characterised and tested as the di-N-methyl-D-glucamine salt

35

Example 148 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-pentafluorophenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

This was prepared essentially as in example 79 except that 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-pentafluorophenylethylamine was used in step a instead of 1S-(3-benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine.

5 1S-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-pentafluorophenylethylamine was prepared by coupling BOC-L-pentafluorophenylalanine with 3,5-dibenzyloxycarbonylaniline using PyBrOP, followed by treatment with trifluoroacetic acid, ¹H NMR (d⁶-DMSO) δ 13.0 (2H, br s), 10.2 (1H, s), 8.9
10 (1H, d), 8.6 (2H, d), 8.5 (1H, t), 8.4 (1H, s), 8.2 (1H, d), 7.9 (1H, s), 7.4 (1H, s), 4.8 (1H, m), 3.5 (1H, dd), 3.2 (1H, dd), 3.0 (2H, d), 1.9 (3H, s), 1.5 (6H, q), 1.4 (6H, s).

15 The compound was further characterised and tested as the di-N-methyl-D-glucamine salt

Example 149 5-(1R-(3,5-dicarboxyphenylaminocarbonyl)-2-pentafluorophenylethylaminocarbonyl)-6-(1-adamantanemethyl-
20 aminocarbonyl)-benzimidazole

This was prepared essentially as in example 79 except that 1R-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-pentafluorophenylethylamine was used in step a instead of 1S-(3-
25 benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine. 1R-(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-pentafluorophenylethylamine was prepared by coupling BOC-pentafluorophenylalanine with 3,5-dibenzyloxycarbonylaniline using PyBrOP, followed by treatment with trifluoroacetic
30 acid, ¹H NMR (d⁶-DMSO) δ 13.0 (2H, br s), 10.2 (1H, s), 8.9 (1H, d), 8.6 (2H, d), 8.5 (1H, t), 8.4 (1H, s), 8.2 (1H, d), 7.9 (1H, s), 7.4 (1H, s), 4.8 (1H, m), 3.5 (1H, dd), 3.2 (1H, dd), 3.0 (2H, d), 1.9 (3H, s), 1.5 (6H, q), 1.4 (6H, s).

35

The compound was further characterised and tested as the di-N-methyl-D-glucamine salt

Example 150 5-(1R-(3,5-dicarboxyphenylaminocarbonyl)-2-(3-fluorophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole

5 This was prepared essentially as in example 79 except that 1R-(3,5-di-benzyloxycarbonylphenylaminocarbonyl)-2-(3-fluorophenyl)ethylamine was used in step a instead of 1S-(3-benzyloxycarbonylphenylaminocarbonyl)-2-phenylethylamine. The 1R-(3,5-di-benzyloxycarbonylphenylaminocarbonyl)-2-(3-
10 fluorophenyl)ethylamine was prepared by coupling BOC-D-3-fluorophenylalanine and 3,5-dibenzyloxycarbonylaniline in the presence of PyBROP, followed by treatment with trifluoroacetic acid, ¹H NMR (d⁶-DMSO) δ 13.0 (3H, br s), 10.2 (1H, s), 8.9 (1H, d), 8.7 (2H, s), 8.5 (1H, t), 8.4
15 (1H, s), 8.2 (1H, s), 7.9 (1H, s), 7.4 (1H, m), 7.2 (4H, m), 4.8 (1H, m), 3.6-2.9 (4H, m), 1.8 (3H, s), 1.7 (6H, q), 1.5 (6H, s).

The compound was further characterised and tested as the di-
20 N-methyl-D-glucamine salt

The compounds of the examples were tested for binding at the CCK_B receptor in mouse cortical membranes by means of a radioligand binding assay. The procedure was as follows:

25

The whole brains from male mice (CD1 22-25g; Charles River) were removed and placed in ice-cold buffer (pH7.2 @ 21 ± 3') of the following composition (mM); 10 HEPES, 130 NaCl, 4.7 KCl, 5 MgCl₂, 1 EDTA and containing 0.25g.l⁻¹ bacitracin.
30 The cortex was dissected, weighed and homogenised in 40ml ice-cold buffer using a Teflon-in-glass homogeniser. The homogenate was centrifuged at 39,800g for 20 min at 4', the supernatant discarded and the pellet resuspended by homogenisation in fresh buffer. The homogenate was
35 recentrifuged (39,800g; 20 min @ 4') and the final pellet was resuspended in HEPES buffer to give a tissue concentration of 2mg.ml⁻¹ (original wet weight).

The membranes (400ml) were incubated for 150 min at $21 \pm 3^\circ$ in a final volume of 0.5ml with HEPES buffer containing [^{125}I]-CCK8S (0.05ml; 200pM NEN 2200Ci.mmol $^{-1}$) and competing compound. Total and non-specific binding of [^{125}I]-CCK8S
5 were defined using 0.05ml of buffer and 0.05ml of 10mM L-365,260, respectively. The assay was terminated by rapid filtration through pre-soaked Whatman GF/B filters using a Brandell Cell harvester. The filters were washed (3 x 3ml) with ice-cold 50mM Tris-HCl (pH7.4 @ 4°C) and bound
10 radioactivity determined by counting (1 min.) in a gamma-counter.

The results obtained from the CCK $_8$ assays are set out in Table 1.

TABLE 1

| Example | CCK ₈ pK _i | Example | CCK ₈ pK _i |
|---------|----------------------------------|---------|----------------------------------|
| 1 | 5.5 | 38 | 7.5 |
| 2 | 5.5 | 39 | 6.4 |
| 3 | 6.4 | 40 | 6.8 |
| 4 | 5.5 | 41 | 7.8 |
| 5 | 6.0 | 42 | 7.8 |
| 6 | 6.0 | 43 | 5.8 |
| 7 | 5.8 | 44 | 8.7 |
| 8 | 5.3 | 45 | 7.1 |
| 9 | 6.6 | 46 | 6.7 |
| 10 | 5.8 | 47 | 6.8 |
| 11 | 5.9 | 48 | 6.2 |
| 12 | 5.9 | 49 | 5.6 |
| 13 | 5.7 | 50 | 6.6 |
| 14 | 6.0 | 51 | 8.0 |
| 15 | 7.9 | 52 | 7.2 |
| 16 | 5.6 | 53 | 8.1 |
| 19 | 5.7 | 54 | 8.1 |
| 20 | 5.0 | 55 | 8.2 |
| 22 | 5.9 | 56 | 7.0 |
| 24 | 8.9 | 57 | 7.7 |
| 26 | 7.9 | 58 | 6.5 |
| 27 | 8.5 | 59 | 6.9 |
| 28 | 8.5 | 60 | 7.8 |
| 29 | 8.1 | 61 | 8.4 |
| 30 | 7.6 | 62 | 7.8 |
| 31 | 7.9 | 63 | 8.4 |
| 32 | 8.4 | 64 | 7.2 |
| 33 | 5.6 | 65 | 7.3 |
| 34 | 8.1 | 66 | 5.8 |
| 35 | 7.2 | 67 | 6.3 |
| 36 | 9.4 | 68 | 5.9 |
| 37 | 8.4 | 69 | 6.5 |

TABLE 1 (contd)

| | Example | CCK ₈ pK _i | Example | CCK ₈ pK _i |
|----|---------|----------------------------------|---------|----------------------------------|
| 5 | 70 | 8.1 | 102 | 7.4 |
| | 71 | 6.4 | 103 | 7.0 |
| | 72 | 6.0 | 104 | 8.9 |
| | 73 | 6.3 | 105 | 8.3 |
| 10 | 74 | 7.6 | 106 | 5.7 |
| | 75 | 7.8 | 108 | 5.9 |
| | 76 | 6.2 | 109 | 6.7 |
| | 77 | 6.6 | 110 | 6.4 |
| | 78 | 7.3 | 111 | 5.8 |
| 15 | 79 | 7.7 | 112 | 8.1 |
| | 80 | 8.4 | 113 | 6.9 |
| | 81 | 6.1 | 114 | 6.0 |
| | 82 | 7.0 | 115 | 7.6 |
| | 83 | 7.8 | 116 | 8.5 |
| 20 | 84 | 8.6 | 117 | 6.1 |
| | 85 | 8.3 | 118 | 6.7 |
| | 86 | 7.5 | 119 | 6.2 |
| | 87 | 9.1 | 120 | 6.2 |
| | 88 | 8.3 | 122 | 8.3 |
| 25 | 89 | 6.2 | 123 | 7.9 |
| | 90 | 8.2 | 124 | 6.5 |
| | 91 | 7.4 | 125 | 8.9 |
| | 92 | 6.5 | 126 | 6.3 |
| | 93 | 8.1 | 127 | 7.6 |
| 30 | 94 | 6.7 | 128 | 8.2 |
| | 95 | 5.9 | 129 | 6.7 |
| | 96 | 6.3 | 130 | 7.6 |
| | 97 | 9.1 | 131 | 8.4 |
| | 98 | 8.4 | 132 | 8.4 |
| 35 | 99 | 8.4 | 134 | 7.6 |
| | 100 | 7.9 | 135 | 8.3 |
| | 101 | 7.4 | 136 | 8.9 |

TABLE 1 (contd)

| | Example | CCK ₈ pK _i | Example | CCK ₈ pK _i |
|---|---------|----------------------------------|---------|----------------------------------|
| 5 | 137 | 7.7 | 139 | 7.8 |
| | 138 | 8.1 | | |

The compounds of the examples were also tested for gastrin antagonist activity in an immature rat stomach assay. The procedure was as follows:

5 The oesophagus of immature rats (33-50 g, ca. 21 days old) was ligated at the level of the cardiac sphincter and the duodenal sphincter was cannulated. The stomach was excised and flushed with ca. 1 ml of unbuffered physiological saline
10 solution. The fundus was punctured and cannulated. A further 4-5 ml of unbuffered solution was flushed through the stomach to ensure the preparation was not leaking. The stomach was lowered into a jacketed organ bath containing 40 ml of buffered solution containing 3×10^{-8} M 5-methyl-
15 furmethide, maintained at 37° and gassed vigorously with 95% O₂/ 5% CO₂. The stomach was continuously perfused at a rate of 1 ml min⁻¹ with unbuffered solution gassed with 100% O₂ with the perfusate passing over an internally referenced pH-electrode fixed 12 cm above the stomach.

20 After 120 min of stabilisation the drugs were added directly to the serosal solution in the organ bath and after a further 60 min cumulative pentagastrin dose-response curves were started. Changes in acid secretion were monitored and
25 the curves analysed according to Black et.al., Br. J. Pharmacol., 1985, 86, 581.

The results obtained from the gastrin assays are set out in Table 2.

30

TABLE 2

| Example | Gastrin pK_b | Example | Gastrin pK_b |
|---------|----------------|---------|----------------|
| 1 | 5.8 | 41 | 7.8 |
| 2 | 6.0 | 42 | 9.3 |
| 3 | 6.7 | 44 | 8.7 |
| 4 | 6.3 | 46 | 7.1 |
| 5 | 6.8 | 47 | 8.3 |
| 7 | 6.4 | 48 | 7.0 |
| 8 | 5.9 | 50 | 6.9 |
| 9 | 6.3 | 51 | 7.6 |
| 10 | 6.5 | 53 | 7.9 |
| 11 | 6.6 | 54 | 8.1 |
| 12 | 5.9 | 55 | 8.3 |
| 13 | 6.4 | 56 | 7.1 |
| 14 | 6.5 | 57 | 7.7 |
| 15 | 8.2 | 58 | 7.5 |
| 16 | 6.2 | 59 | 7.5 |
| 21 | 5.3 | 60 | 8.1 |
| 23 | 7.4 | 61 | 8.7 |
| 24 | 9.5 | 62 | 8.2 |
| 26 | 9.3 | 63 | 9.1 |
| 27 | 9.2 | 65 | 8.2 |
| 28 | 9.7 | 67 | 6.8 |
| 29 | 9.2 | 69 | 7.1 |
| 30 | 9.1 | 70 | 7.8 |
| 31 | 8.9 | 71 | 7.0 |
| 32 | 9.1 | 72 | 6.3 |
| 33 | 7.7 | 73 | 7.2 |
| 34 | 8.7 | 74 | 9.0 |
| 35 | 8.7 | 75 | 7.7 |
| 37 | 8.4 | 76 | 6.9 |
| 38 | 7.1 | 77 | 7.0 |
| 39 | 6.8 | 78 | 8.6 |
| 40 | 7.3 | 79 | 7.0 |

TABLE 2 (contd)

| Example | Gastrin pK _s | Example | Gastrin pK _s |
|---------|-------------------------|---------|-------------------------|
| 80 | 8.2 | 112 | 8.2 |
| 81 | 6.9 | 113 | 7.2 |
| 82 | 6.9 | 115 | 8.2 |
| 83 | 7.2 | 116 | 9.0 |
| 85 | 8.9 | 118 | 6.7 |
| 86 | 7.7 | 122 | 9.1 |
| 87 | 9.6 | 123 | 8.5 |
| 88 | 8.6 | 124 | 6.8 |
| 89 | 6.8 | 125 | 9.4 |
| 90 | 8.0 | 126 | 7.0 |
| 91 | 8.0 | 127 | 7.5 |
| 92 | 6.8 | 128 | 8.6 |
| 93 | 7.7 | 131 | 9.7 |
| 95 | 5.9 | 132 | 9.0 |
| 100 | 7.5 | 133 | 8.1 |
| 103 | 7.8 | 134 | 8.8 |
| 104 | 8.6 | 135 | 8.9 |
| 105 | 8.5 | 136 | 9.5 |
| 108 | 6.1 | 137 | 7.8 |
| 109 | 6.9 | 139 | 7.1 |
| 110 | 6.9 | | |

The compounds of the examples were also tested in a CCK₈ binding assay as follows:

- 5 The pancreatata were removed from male guinea-pigs (200-300g; Dunkin Hartley) and placed in ice-cold HEPES buffer (pH 7.2 @ 21 ± 3°). The pancreatata were homogenised in 40 ml ice-cold HEPES buffer using a polytron (Brinkmann, PT10, setting 10) 4 x 1 second. The homogenate was centrifuged at
- 10 39,800g for 15 min at 4°. The supernatant was discarded and the pellet re-suspended using a Teflon-in-glass homogeniser in 20 volumes of fresh buffer and re-centrifuged as above.

The final pellet was re-suspended using a Teflon-in-glass homogeniser to a tissue concentration of 1 mg.ml^{-1} (original wet weight), and filtered through $500 \text{ }\mu\text{m}$ pore-size Nytex mesh.

5

The membranes ($400\mu\text{l}$; containing $0.375 \text{ }\mu\text{M}$ PD134,308) are incubated for 150 minutes at $21 \pm 3^\circ$ in a final volume of 0.5ml with HEPES buffer containing $[^{125}\text{I}]\text{-CCK}_8(\text{S})$ ($50\mu\text{l}$; 200pM) and competing compound. Total and non-specific
10 binding of $[^{125}\text{I}]\text{-CCK}_8(\text{S})$ are defined using $50\mu\text{l}$ of buffer and $50\mu\text{l}$ of 100nM L-364,718 respectively. The assay is terminated by rapid filtration through pre-soaked Whatman GF/B filters using a Brandell Cell Harvester. The filters were washed ($3 \times 3\text{ml}$) with ice-cold 50mM Tris HCl ($\text{pH } 7.4$ at
15 4°) and bound radioactivity is determined by counting (1 min) in a gamma counter.

The results are set out in Table 3.

TABLE 3

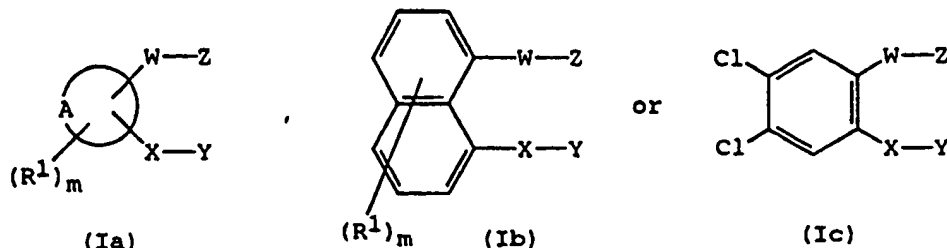
| Example | CCK _A pK _i | Example | CCK _A pK _i |
|---------|----------------------------------|---------|----------------------------------|
| 1 | 5.1 | 45 | 6.1 |
| 2 | 4.9 | 46 | 5.1 |
| 3 | 5.5 | 47 | 5.2 |
| 4 | 5.4 | 48 | 5.5 |
| 5 | 5.2 | 49 | 5.6 |
| 6 | 5.6 | 50 | 6.1 |
| 7 | 5.8 | 52 | 5.9 |
| 8 | 6.0 | 53 | 6.1 |
| 15 | 6.1 | 54 | 5.9 |
| 16 | 5.5 | 55 | 5.8 |
| 17 | 4.8 | 57 | 5.7 |
| 18 | 6.3 | 58 | 5.0 |
| 19 | 5.3 | 59 | 5.1 |
| 20 | 5.0 | 60 | 5.6 |
| 21 | 5.2 | 61 | 5.2 |
| 22 | 5.4 | 62 | 5.4 |
| 24 | 5.7 | 66 | 5.0 |
| 26 | 5.5 | 67 | 5.7 |
| 27 | 5.6 | 68 | 5.9 |
| 28 | 5.4 | 69 | 5.1 |
| 29 | 5.4 | 70 | 5.1 |
| 30 | 5.2 | 71 | 5.3 |
| 31 | 5.5 | 72 | 5.6 |
| 33 | 5.2 | 73 | 5.2 |
| 34 | 6.1 | 74 | 5.3 |
| 36 | 5.5 | 75 | 6.1 |
| 37 | 5.6 | 76 | <5.0 |
| 39 | 4.9 | 77 | <5.0 |
| 40 | 6.3 | 78 | 5.3 |
| 41 | 5.7 | 79 | 6.0 |
| 42 | 5.5 | 80 | 6.1 |
| 44 | 5.6 | 81 | 5.5 |

TABLE 3 (contd)

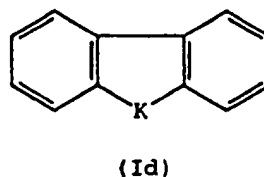
| Example | CCK _A pK _i | Example | CCK _A pK _i |
|---------|----------------------------------|---------|----------------------------------|
| 82 | 5.7 | 111 | <5.0 |
| 83 | 6.4 | 112 | <5.0 |
| 84 | 6.2 | 113 | 5.2 |
| 85 | 5.5 | 114 | 5.5 |
| 86 | 5.0 | 115 | 5.6 |
| 87 | 5.5 | 116 | 5.6 |
| 88 | 5.6 | 117 | 5.8 |
| 89 | 5.1 | 118 | 6.3 |
| 90 | 5.3 | 119 | 5.6 |
| 91 | 5.3 | 120 | 6.0 |
| 92 | 4.9 | 121 | 5.1 |
| 93 | 5.6 | 122 | 5.4 |
| 94 | 5.0 | 123 | 6.3 |
| 95 | 5.8 | 124 | 5.7 |
| 96 | 5.7 | 125 | 5.7 |
| 97 | 6.3 | 126 | 5.3 |
| 98 | 6.7 | 127 | 5.9 |
| 99 | 5.4 | 128 | 5.7 |
| 100 | 6.4 | 129 | 5.1 |
| 101 | 6.6 | 130 | 5.4 |
| 102 | 5.9 | 131 | 5.3 |
| 103 | 5.2 | 132 | 5.4 |
| 104 | 6.5 | 133 | 5.1 |
| 105 | 6.8 | 134 | 6.1 |
| 108 | <5.0 | 135 | 5.1 |
| 109 | <5.0 | 136 | <5.0 |
| 110 | <5.0 | | |

CLAIMS

1. A compound of the formula



5 wherein A represents a group having two fused rings, in which the atoms which are common to the two rings are joined by a single or multiple bond, W and X replacing hydrogen on adjacent atoms, or A is a group of the formula



10 in which W and X replace hydrogen on adjacent carbon atoms,

m is from 0 to 6, provided that m is not more than 2 unless R¹ is exclusively halo,

15 R¹ is halo, amino, amidino, nitro, cyano, hydroxy, sulphamoyl, hydroxysulphonyl, carboxy, esterified carboxy, amidated carboxy, tetrazolyl, C₁ to C₈ alkyl, aryl, substituted aryl, C₁ to C₆ hydroxyalkyl, C₁ to C₆ haloalkyl, C₁ to C₆ alkoxy, C₁ to C₆ alkylcarboxyamino, HON=C-,
 20 R²⁷-SO₂-NH-, R²⁷-SO₂-NH-CO-, R²⁷-CO-, R²⁷-CO-NH-, R²⁷-CO-NH-SO₂-, R²⁷-CO-NH-SO- or R²⁸-NH-SO₂-, wherein R²⁷ is H (except when R²⁷ is attached to a sulphur atom), C₁ to C₆ alkyl, C₁ to C₆ haloalkyl, aryl or substituted aryl, and R²⁸ is H, C₁ to C₆ alkyl, C₁ to C₆ haloalkyl, aryl, substituted aryl, -OH or
 25 -CN (each R¹ group, when m is 2 or more, being independently selected from the foregoing),

K represents -O-, -S-, -CH₂-, -N(R²)- or -N(COR²)-, in which R² is H or C₁ to C₃ alkyl,

W is a carbonyl, sulphonyl or sulphinyl group, and X is a carbonyl, sulphonyl or sulphinyl group, provided that at least one of W and X contains carbonyl,

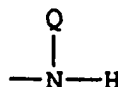
Y is R³-N(R⁴)- or R³'-O- (wherein R³ is H or C₁ to C₁₅ hydrocarbyl, one or more hydrogen atoms of the hydrocarbyl moiety optionally being replaced by halogen atoms, and up to two carbon atoms of the hydrocarbyl moiety optionally being replaced by a nitrogen, oxygen or sulphur atom, R³' is C₆ to C₁₅ hydrocarbyl, one or more hydrogen atoms of the hydrocarbyl moiety optionally being replaced by halogen atoms, and up to two carbon atoms of the hydrocarbyl moiety optionally being replaced by a nitrogen, oxygen or sulphur atom, and R⁴ is H, C₁ to C₃ alkyl, carboxymethyl or esterified carboxymethyl), provided that Y does not contain a -O-O- group, and

Z is selected from

i) -O-R^5

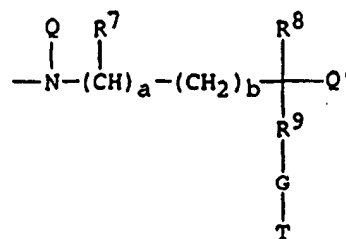
wherein R⁵ is H, C₁ to C₅ alkyl, phenyl, substituted phenyl, benzyl or substituted benzyl;

ii)



wherein Q is H, C₁ to C₅ hydrocarbyl, or -R⁶-U, wherein R⁶ is a bond or C₁ to C₅ alkylene and U is aryl, substituted aryl, heterocyclic, substituted heterocyclic or cycloalkyl,

iii)



wherein a is 0 or 1 and b is from 0 to 3,

R⁷ is H or methyl,

5

R⁸ is H or methyl; or R⁸ is CH₂= and Q' is absent; or R⁷ and R⁸ are linked to form a 3- to 7-membered ring,

R⁹ is a bond or C₁ to C₅ hydrocarbylene,

10

G is a bond, -CHOH- or -C(O)-

Q' is as recited above for Q or -R⁶-(C(O))_d-L-(C(O))_e-R⁵ (wherein R⁵ and R⁶ are as defined above, L is O, S or -N(R¹⁰)-, in which R¹⁰ is as defined above for R⁴, and d and e are 0 or 1, provided that d+e<2); or Q' and R⁸, together with the carbon atom to which they are attached, form a 3- to 7-membered ring,

15

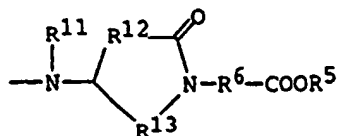
20

Q is as defined above; or Q and R⁸ together form a group of the formula -(CH₂)_f-V-(CH₂)_g- wherein V is -S-, -S(O)-, -S(O)₂-, -CH₂-, -CHOH- or -C(O)-, f is from 0 to 2 and g is from 0 to 3; or, when Q' is -R⁶-U and U is an aromatic group, Q may additionally represent a methylene link to U, which link is ortho to the R⁶ link to U,

25

T is H, cyano, C₁ to C₄ alkyl, -CH₂OH, carboxy, esterified carboxy, amidated carboxy or tetrazolyl; or

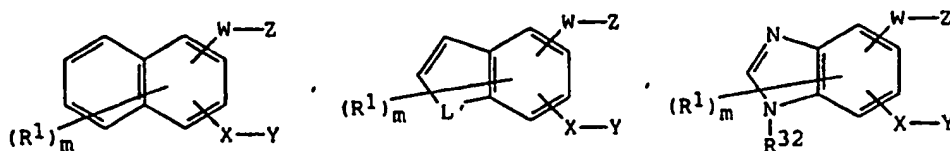
iv)



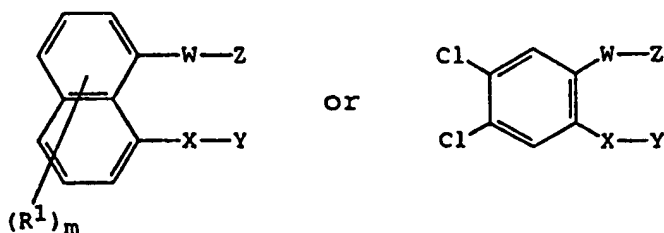
wherein R^5 and R^6 are as defined above, R^{11} is as defined above for R^4 , and R^{12} and R^{13} are independently a bond or C_1 to C_3 alkylene, provided that R^{12} and R^{13} together provide from 2 to 4 carbon atoms in the ring,

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, of the formula



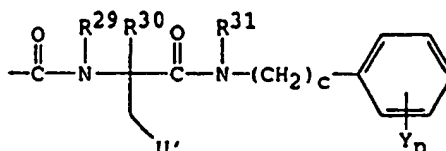
(wherein W and X are attached to adjacent carbon atoms; R^{32} is H, C_1 to C_3 alkyl or C_1 to C_3 alkylcarboxy; and L' is $-NR^{32}-$, $-O-$ or $-S-$),



wherein W, X, Y, Z, R^1 and m are as defined in claim 1.

3. A compound according to claim 1 or claim 2 wherein R^3 is C_6 to C_8 straight or branched chain alkyl, or $R^{23}-(CH_2)_p-$, wherein R^{23} is selected from phenyl, 1-naphthyl, 2-naphthyl, indolyl, norbornyl, adamantyl, cyclohexyl or cycloheptyl, and p is from 0 to 3.

4. A compound according to any of claims 1 to 3 wherein W is carbonyl and X is sulphonyl.
5. A compound according to any of claims 1 to 3 wherein W is carbonyl and X is carbonyl.
6. A compound according to any of claims 1 to 3 wherein W is sulphonyl and X is carbonyl.
7. A compound according to any preceding claim wherein m is 0.
8. A compound according to claim 1 wherein
- 15 -X-Y is -CONR³R⁴ (R³ and R⁴ being as defined in claim 1), and
-W-Z is



- (wherein R²⁹, R³⁰ and R³¹ are independently H or C₁ to C₃ alkyl; U' is an (optionally substituted) aromatic group; n is 1 or 2; Y is -CO₂H, tetrazolyl, esterified carboxy, amidated carboxy, R²⁷-SO₂-NH-, R²⁷-SO₂-NH-CO-, R²⁷-CO-, R²⁷-CO-NH-, R²⁷-CO-NH-SO₂-, R²⁷-CO-NH-SO- or R²⁸-NH-SO₂- (R²⁷ and R²⁸ being as defined in claim 1), each Y being independently selected from the foregoing when n is 2; and c is from 0 to 2).
9. A compound selected from 5-(1S-(3,5-dicarboxyphenylamino-carbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole, 5-(1R-(3,5-dicarboxyphenylamino-carbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole, 5-(1R-(3,5-dicarboxyphenylamino-carbonyl)-2-(2-fluorophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole, 5-(1S-(3,5-dicarboxy-

phenylaminocarbonyl)-2-(2-fluorophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole, 5-(1R-(3,5-dicarboxyphenylaminocarbonyl)-2-(4-hydroxyphenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole, 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-(4-hydroxyphenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-indole, 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole, 5-(1R-(3,5-dicarboxyphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole, 5-(1R-(3,5-dicarboxyphenylaminocarbonyl)-2-(2-fluorophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole, 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-(2-fluorophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole, 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-(3-fluorophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole, 5-(1R-(3,5-dicarboxyphenylaminocarbonyl)-2-(3-fluorophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole, 5-(1R-(3,5-dicarboxyphenylaminocarbonyl)-2-(4-hydroxyphenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole, 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-(4-hydroxyphenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole, 5-(1S-(3,5-dicarboxyphenylaminocarbonyl)-2-(2-fluorophenyl)ethylaminocarbonyl)-6-(cycloheptanemethylaminocarbonyl)-benzimidazole, 5-(1S-(3-benzoylamino sulphonylphenylaminocarbonyl)-2-phenylethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole, and 5-(1S-(3-benzoylamino sulphonylphenylaminocarbonyl)-2-(2-fluorophenyl)ethylaminocarbonyl)-6-(1-adamantanemethylaminocarbonyl)-benzimidazole.

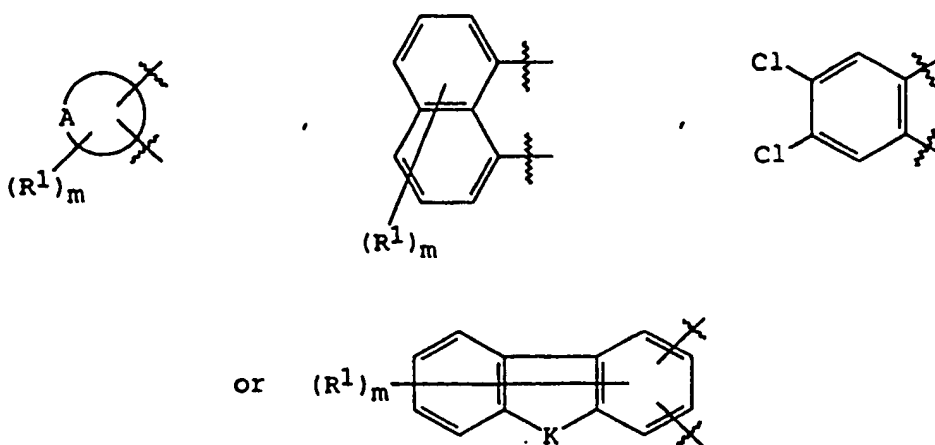
10. A pharmaceutical composition comprising a compound according to any preceding claim, together with a pharmaceutically acceptable diluent or carrier.

11. A method of making a compound according to claim 1

wherein W is carbonyl, said method including the step of reacting a compound of the formula YH (wherein Y is as defined in claim 1) with a compound of the formula



5 wherein B represents



and A, R¹, m, K, and X are as defined in claim 1.

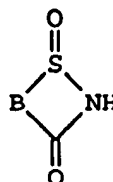
12. A method of making a compound according to claim 1
 10 wherein W is sulphonyl, said method comprising the step of reacting a compound of the formula R¹-Hal with a compound of the formula



15 wherein Hal represents a halogen atom and B and R¹ are as defined in claim 1, and then reacting the product with an alkoxide.

13. A method of making a compound according to claim 1 wherein W or X is sulphoxide, said method comprising the step of reacting a compound of the formula $R^3\text{-Hal}$ with a compound of the formula:

5



(XI)

wherein Hal represents a halogen atom and B and R^3 are as defined in claim 1, and then reacting the product with an alkoxide.

10 14. A method of making a pharmaceutical composition according to claim 10, comprising mixing a compound according to any of claims 1 to 9 with a pharmaceutically acceptable diluent or carrier.